Long-term lifestyle and dietary habits in relation to cardiovascular mortality and life expectancy:

a prospective cohort study

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a prospective cohort study

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Abstract

Introduction: In prospective cohort studies, information on lifestyle and dietary habits is generally only assessed at the baseline examination, assuming that these habits are relatively constant over the entire study period. Repeated measures can take into account changes in these habits, reduce measurement error due to a reduction in within-subject variation, and can give more insight into the etiology of diseases. The main objective of this thesis is to assess the relationships of recent and long-term exposure to known lifestyle and dietary risk factors with cardiovascular mortality and life expectancy.

Methods: We used data from the Zutphen Study, a prospective cohort study among 1373 men born between 1900 and 1920. These men were examined repeatedly in seven examination rounds between 1960 and 2000. In addition to hazard ratios (HR), we presented some of our results in terms of differences in life expectancy at age 50.

Main findings on lifestyle factors: We found that both the number of cigarettes smoked and smoking duration were strongly associated with mortality risk. Compared to never or long-term former smoking, cigarette smoking decreased life expectancy by about 7 years and exclusive cigar or pipe smoking decreased life expectancy by about 5 years. Stopping smoking cigarettes at age 50 increased life expectancy by 3.3 years. Furthermore, we observed that long-term light alcohol intake, i.e. ≤20 grams per day, compared to no alcohol intake, lowered cardiovascular (HR: 0.70 [95% confidence interval: 0.55 to 0.89]) and all-cause (HR: 0.75 [0.63 to 0.91]) mortality risk. Compared to men who do not consume alcohol, wine consumers had a 5 years longer life expectancy.

Main findings on dietary factors: We observed that average *trans* unsaturated fatty acid intake decreased from 7 to about 1 percent of energy intake between 1960 and 2000 and that each additional 2 percent of long-term energy intake from *trans* unsaturated fatty acids was positively associated with sudden coronary death (HR: 1.62 [1.01 to 2.60]). In contrast, long-term fatty fish consumption was inversely associated with sudden coronary death (HR: 0.46 [0.27 to 0.78]). The strength of the association between long-term total fish consumption and coronary heart disease (CHD) death decreased from age 50 (HR: 0.32 [0.13 to 0.80]) until age 80 (HR: 1.34 [0.58 to 3.12]). We observed no clear dose-response relationship between the intake of the n-3 fatty acids EPA and DHA, and (sudden) coronary death. Finally, we found that each additional 10 grams of recent dietary fiber intake was associated with a lower risk of CHD (HR: 0.83 [0.70 to 0.98]) and all-cause (HR: 0.91 [0.82 to 1.00]) mortality.

Conclusions: The studies described in this thesis emphasize the importance of lifestyle and diet for public health. Our results suggest that non-smoking and a low level of wine consumption decrease the risk of (cardiovascular) mortality and will increase life expectancy at age 50. The long-term consumption of fatty fish and the reduction in long-term *trans* unsaturated fatty acid intake may prevent sudden coronary deaths, and a higher recent dietary fiber intake may reduce both CHD and all-cause mortality risk.

Table of contents

Chapter 1	General introduction	9
Chapter 2	Mortality and life expectancy in relation to long-term cigarette, cigar and pipe smoking: The Zutphen Study *Tob Control 2007;16:107-13*	21
Chapter 3	Long-term wine consumption is independently of moderate alcohol intake related to cardiovascular mortality and life expectancy: The Zutphen Study *J Epidemiol Community Health, accepted for publication*	37
Chapter 4	Long-term *trans* unsaturated fatty acid intake and 40-y (sudden) coronary heart disease death: The Zutphen Study *Submitted for publication*	53
Chapter 5	Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen Study *Eur Heart J 2008;29:2024-30*	65
Chapter 6	Dietary fiber in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study *Am J Clin Nutr 2008;88:1119-25*	81
Chapter 7	General discussion	97
Summary in English		111
Summary in Dutch (Samenvatting)		115
Acknowledgements (Dankwoord)		119
About the author		123

Chapter 1

General introduction

Introduction

Changes in life expectancy

Between 1960 and 1970, life expectancy at birth among Dutch men was relatively constant, i.e. about 71 years. After that, life expectancy at birth increased steadily to 78 years in 2007 (**figure 1.1**). For life expectancy at age 50, the same trend was seen. A major determinant for the increase in life expectancy is the decrease in risk of dying from cardiovascular diseases, such as coronary heart disease and cerebrovascular diseases (1). It is expected that, for men, life expectancy at birth will increase to 81.5 years in 2050 (2).

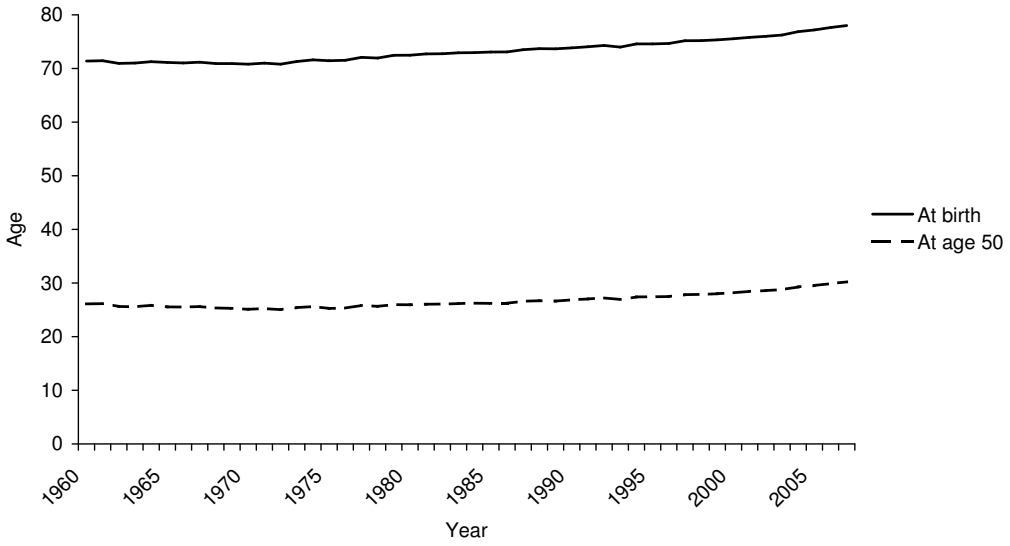

Figure 1.1. Life expectancy at birth and age 50 among men from 1960 through 2007 (Source: CBS Statline).

Cardiovascular and (sudden) coronary heart disease

In the Netherlands, cardiovascular diseases (CVD) are the second leading cause of death among men. In 1980, more than 50% of the men dying from CVD, died from coronary heart disease (CHD) and about 20% died from cerebrovascular diseases **(figure 1.2)** (3). In 2007, about one-third of the men died from CHD and another one-third from cerebrovascular diseases (3). CHD is characterized by a lack of blood and oxygen in the heart and surrounding tissue. Atherothrombosis is the underlying process for the occurrence of CHD. The clinical manifestations of atherosclerosis are the consequence of thrombotic complications on disrupted or ruptured atherosclerotic lesions. The risk of suffering a thrombotic complication depends more on the composition and instability of the atherosclerotic lesions than their stenotic severity (4-6). Major risk factors for CHD are age, genetics (7), unhealthy diet (8), lack of physical activity (9), smoking (10), high alcohol intake (11), obesity (12), diabetes mellitus (13), high blood pressure (14), high LDL cholesterol and low HDL cholesterol (15;16), and high levels of inflammation markers such as C-reactive protein (17). Changes in these risk factors, especially the large decrease in the percentage smokers (18;19) and serum cholesterol levels (18), and the

improvement in treatment (19), are responsible for the remarkable decrease in CVD and CHD mortality in the Netherlands in the past 30 years (figure 1.2).

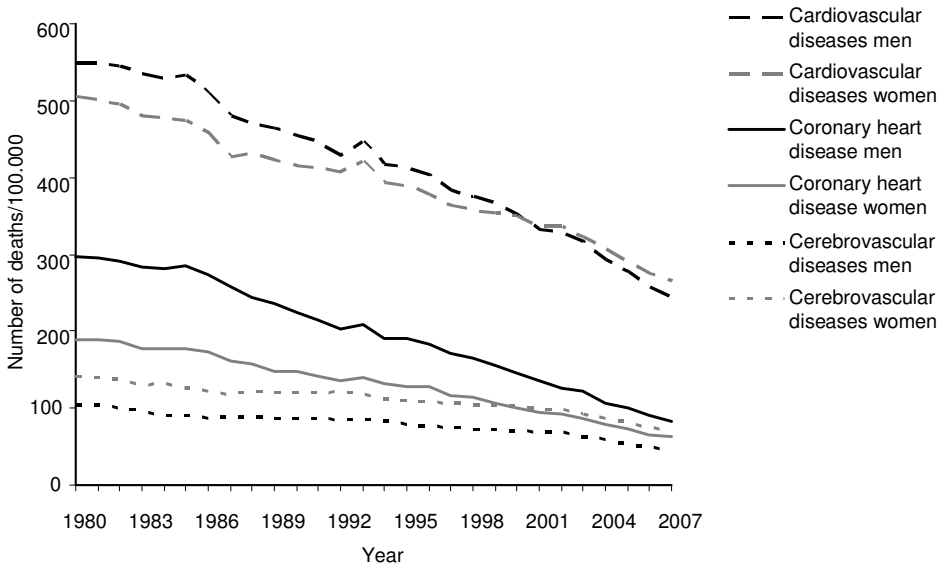

Figure 1.2. Trends in age-standardized number of deaths (year of standardization: 2007) due to cardiovascular diseases, coronary heart disease and cerebrovascular diseases in the Netherlands between 1980 and 2007 (3).

About 50% of coronary heart disease deaths are sudden. Sudden cardiac death is defined as a natural, nonviolent, unexpected death due to cardiac causes, and occurring within one hour of the onset of acute symptoms (20). A sub-classification to distinguish 'coronary' from 'noncoronary' sudden cardiac deaths has been proposed. The time until death after onset of symptoms was originally 24 hours but has been set to one hour or even an instantaneous event to account for a more likely arrhythmic mechanism (21;22). As a consequence, definitions of sudden cardiac death may vary between studies. In most cases of sudden cardiac death, the underlying mechanism is ventricular fibrillation caused by coronary atherosclerosis (21;22). The risk of sudden cardiac death is the highest within 6 to 18 months after a primary cardiac event; thereafter, the risk decreases (23). In general, risk factors for sudden cardiac death seem the same as those for atherosclerotic coronary disease (22), but need further study.

Lifestyle factors, cardiovascular mortality and life expectancy

Smoking habits and alcohol consumption are major risk factors for cardiovascular diseases and strong determinants of life expectancy.

Smoking habits

Smoking has been recognized as a major health hazard for many years. Smoking causes a wide range of diseases including CVD, cancer, and chronic obstructive pulmonary diseases (COPD). Smoking cessation has impressive health benefits (24-26). Cigarette smoking cessation decreases the risk of chronic diseases, but stopping smoking at age 50 increases life expectancy with about 6 years. Even stopping at age 60 gains about 3 years of life expectancy (27).

Since smoking habits change during life, information on long-term smoking history is therefore required to get correct estimates of the long-term health effects of smoking. Because in most studies the level of detail on smoking history is limited, the impact of various aspects of the smoking history remains unclear. Leffondré *et al.* (28) show the importance of information on smoking duration, intensity and time since cessation in this respect. Although smoking duration has been associated with mortality in earlier studies, the majority focused on cancer mortality rather than on CVD and COPD mortality (29-35). Moreover, little is known about the adverse health effects of long-term cigar or pipe smoking (36-38).

Alcohol consumption

Results of prospective studies show a U- or J-shaped relationship between alcohol intake and all-cause mortality (39). This association can be explained by a lower risk of CVD mortality in light to moderate drinkers compared to heavy drinkers and abstainers (40-43). The protective effect of light to moderate alcohol intake may be due to an increase in HDL cholesterol and prevention of blood clotting and reduction of platelet aggregation (44;45). Red wine consumption may have an additional health benefit because of its polyphenolic compounds (46;47) that interfere with the initiation, progression and rupture of atherosclerotic plaques (48), and improve endothelial function (49;50). Although some epidemiological studies showed beneficial effects of wine consumption (51;52), results of several other studies do not show an advantage of one type of alcoholic beverage over another (53). The effects of long-term amount of alcohol intake and type of alcoholic beverage on cardiovascular mortality and life expectancy need further study.

Diet and (sudden) coronary mortality

According to the classic diet-heart hypothesis, the consumption of saturated fatty acids and dietary cholesterol raises plasma (LDL) cholesterol levels, thereby causing coronary heart disease (54). However, more recent studies have shown that the increased risk of CHD is not only due to an increase in (LDL) cholesterol levels but also to other factors like inflammation (55-57) **(figure 1.3)**. Moreover, the intake of other dietary factors, among which *trans* unsaturated fatty acids, n-3 fatty acids, and dietary fiber (8), may influence the risk of CHD (figure 1.3).

***Trans* unsaturated fatty acids**

Results from several studies suggest that *trans* unsaturated fatty acids are strongly associated with the risk of CHD. This is consistent with findings from clinical trials showing that these fatty acids increase LDL cholesterol and lower HDL cholesterol concentrations in blood (58) and negatively affect other risk factors such as inflammation and endothelial function (59). In prospective studies, each 2% increase in energy intake from *trans* unsaturated fatty acids was

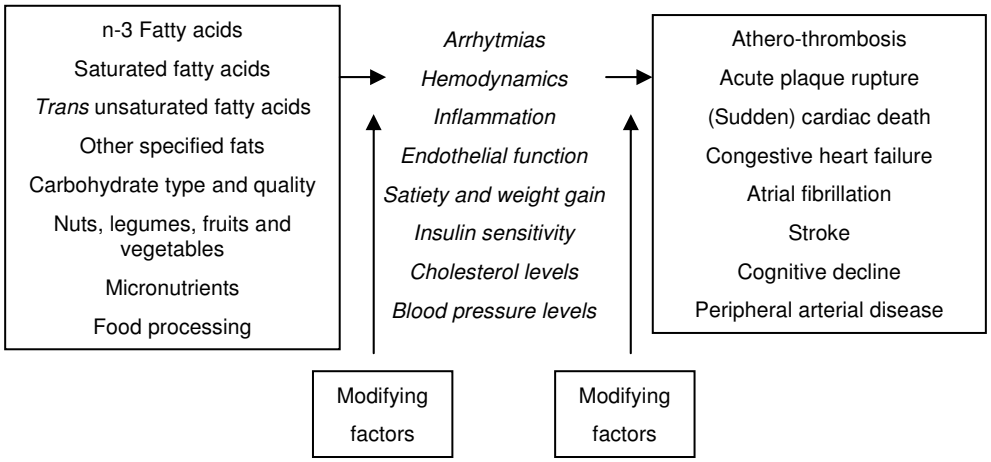

Figure 1.3. Effects of dietary factors on intermediate risk factors and cardiovascular outcomes (adapted from reference 67).

associated with a 23% increase in the incidence of CHD (60). However, little is known about the effects of *trans* unsaturated fatty acid intake on sudden coronary death.

Fish consumption

In contrast to the adverse effects of *trans* unsaturated fatty acids, consuming a relatively small amount of fish or fish oil was associated with a lower risk of CHD death (61-65). Eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA), two very long-chain n-3 polyunsaturated fatty acids mainly found in fatty fish, are the constituents in fish oil that may reduce the risk of CHD death. The most likely explanation by which relatively small amounts of EPA and DHA reduce the risk of CHD death are their anti-arrhythmic properties (66). In a meta-analysis of cohort studies, He *et al*. estimated that consuming fish once a week lowers CHD death risk by 15% (65). In addition, Mozaffarian and Rimm estimated, by combining results from both randomized trials and large prospective cohort studies, that consuming 250 mg EPA+DHA per day lowers CHD death risk by 36% (64;67). Moreover, long-chain n-3 fatty acids are also suggestive for an inverse relation with sudden cardiac death (68;69). In observational studies, consuming fish once or twice a week was associated with a 42-50% lower risk of sudden cardiac death or cardiac arrest (70-72). The associations with blood or cell membrane (71) levels of EPA+DHA were even stronger. More research is needed on the effect of long-term fish consumption or EPA+DHA intake on (sudden) coronary deaths.

Dietary fiber intake

Epidemiological studies have shown that consumption of (whole grain) cereals (73-76), vegetables and fruit (77-80) may lower the risk of CHD mortality. Dietary fiber is one of the components that may be responsible for the beneficial effects of these foods. Results from intervention trials have shown that (water-soluble) dietary fiber may lower blood cholesterol levels (81), reduce blood pressure (82;83), promote body weight loss (84) and may improve insulin sensitivity (85), and thereby lower the risk of CHD mortality (86-89). In a pooled analysis of cohort studies, total dietary fiber intake was inversely associated with the risk

of CHD mortality (86). Furthermore, the intake of dietary fiber from cereals and fruits was, independent of each other, inversely associated with the risk of CHD mortality (86). However, the effects of long-term dietary fiber intake on coronary and all-cause mortality need further investigation.

Long-term exposure

Lifestyle habits and food consumption patterns usually change during the course of life and may affect the diet-disease relationship. However, in prospective cohort studies, information on lifestyle factors and food consumption is generally only assessed at the baseline examination, assuming that these habits are relatively constant over the entire study period. Repeated measures of lifestyle factors and food consumption over a longer period of time can take into account changes in these habits. Moreover, the use of repeated measures, especially an average exposure, reduces measurement error due to a reduction in within-subject variation over time (90). Furthermore, the use of repeated measures can give more insight into the etiology of diseases. An average or long-term exposure may be etiologically more relevant than baseline or most recent exposure (90;91).

Rationale and outline of the thesis

The main objective of this thesis is to assess the relationships of recent and long-term exposure to known lifestyle and dietary risk factors with cardiovascular mortality and life expectancy. For this purpose, we used data from the Zutphen Study, a prospective cohort study among men born between 1900 and 1920 and residing for at least 5 years in Zutphen, The Netherlands. These men were examined repeatedly between 1960 and 2000. We used up to seven repeated measures of lifestyle factors and dietary habits to take into account changes in these habits during the follow-up period, and to reduce measurement error. Moreover, we used the repeated measures to assess whether an average or long-term exposure is more important than a recent exposure in the etiology of cardiovascular and all-cause mortality.

In epidemiological studies, hazard ratios are commonly used to express the impact on mortality. Since hazard ratios express effects for an exposed group relative to the effect of the unexposed group, they do not provide information regarding absolute health effects. Such insight can be obtained by the calculation of life expectancies and the number of life-years lost. Although concepts like life expectancy are more informative and easier to understand, they are not reported frequently. Therefore, we present our results also in terms of differences in life expectancy at age 50 in addition to hazard ratios.

We describe the relationships of long-term cigarette, cigar or pipe smoking, and duration and the number of cigarettes smoked, with cardiovascular mortality and life expectancy in **chapter 2**. The impact of long-term alcohol intake and different types of alcoholic beverages consumed on cardiovascular mortality and life expectancy is estimated in **chapter 3**. **Chapter 4** describes the changes in *trans* unsaturated fatty acid intake between 1960 and 2000. Moreover, we relate long-term *trans* unsaturated fatty acid intake (**chapter 4**) and fish consumption or EPA+DHA intake (**chapter 5**) to (sudden) coronary mortality. In **chapter 6**, the impact of recent and long-term dietary fiber intake on coronary and all-cause mortality is described. Finally, the

main findings, methodological considerations, public health implications, and suggestions for future research are discussed in **chapter 7**.

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Chapter 2

Mortality and life expectancy in relation to long-term cigarette, cigar and pipe smoking: The Zutphen Study

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Abstract

Study objective: To study the effect of long-term smoking on all-cause and cause-specific mortality, and to estimate the effects of cigarette and cigar or pipe smoking on life expectancy.
Design: A long-term prospective cohort study.
Setting: Zutphen, The Netherlands.
Participants: 1373 men from the Zutphen Study, born between 1900 and 1920 and studied between 1960 and 2000.
Measurements: Hazard ratios for type of smoking, amount and duration of cigarette smoking, obtained from a time-dependent Cox regression model. Absolute health effects of smoking are expressed as differences in life expectancy and the number of disease-free years of life.
Main results: Duration of cigarette smoking was strongly associated with mortality from cardiovascular diseases, lung cancer and chronic obstructive pulmonary disease, whereas both the number of cigarettes smoked as well as duration of cigarette smoking were strongly associated with all-cause mortality. Average cigarette smoking reduced the total life expectancy by 6.8 years, whereas heavy cigarette smoking reduced the total life expectancy by 8.8 years. The number of total life-years lost due to cigar or pipe smoking was 4.7 years. Moreover, cigarette smoking reduced the number of disease-free life-years by 5.8 years, and cigar or pipe smoking by 5.2 years. Stopping cigarette smoking at age 40 increased the life expectancy by 4.6 years, while the number of disease-free life-years was increased by 3.0 years.
Conclusions: Cigar or pipe smoking reduces life expectancy to a lesser extent than cigarette smoking. Both the number of cigarettes smoked and duration of smoking are strongly associated with mortality risk and the number of life-years lost. Stopping smoking after age 40 has major health benefits.

Introduction

Smoking has been recognized as a health hazard for many years. Smoking causes a wide range of diseases including cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVD), and smoking cessation has impressive health benefits (1-3). Cigarette smoking cessation decreases the risk of diseases and also increases life expectancy. Even stopping at age 60 gains about 3 years of life expectancy (4). Much less is known about the adverse effects of long-term cigar or pipe smoking (5-7).

Smoking has both long- and short-term effects. As smoking habits change during life, information on long-term smoking history is required to obtain correct estimates of the long-term health effects of smoking. Because in most studies the level of detail on smoking history is limited, the impact of various aspects of the smoking history remains unclear. Leffondré *et al.* (8) show the importance of information on smoking duration, intensity and time since cessation in this respect. Although smoking duration has been associated with mortality before, most studies focused on cancer mortality rather than CVD and COPD mortality (9-15).

In epidemiological studies, hazard ratios are commonly used to express the impact on mortality. Hazard ratios express effects for one exposure group relative to the effect of the unexposed group –that is, the reference group– but do not give information regarding absolute public health effects. Therefore, life expectancies should be calculated. Although concepts like life expectancy are more informative and readily grasped by all, they are not reported frequently.

The objective of this study is to asses the relationships between long-term cigarette, cigar or pipe smoking, and duration and the number of cigarettes smoked, and mortality. To obtain accurate effect estimates, we used repeated measures of smoking habits collected in a 40-year period and adjusted for potential confounders. In addition to hazard ratios, we present our results also in terms of changes in life expectancy at age 40 and the number of disease-free years of life due to cigarette and cigar or pipe smoking.

Materials and methods

Study population

The Zutphen Study was started as the Dutch contribution to the Seven Countries Study, a longitudinal study of the relationships between diet, other risk factors and chronic diseases (16). The Zutphen Study has been carried out since 1960 among middle-aged men in Zutphen, an old industrial town in the eastern part of the Netherlands with about 25 000 inhabitants. In 1960, a random sample was drawn of 1088 men born between 1900 and 1919 and residing for at least 5 years in Zutphen. Of these, 878 (81%) men participated in the Zutphen Study and 872 men took part in both dietary and medical examinations. The examinations were repeated in 1965, 1970, 1985, 1990, 1995 and 2000. In 1985, the group of 554 survivors was extended with a new random sample of men of the same age. Of the 1266 men who were invited, 939 (74%) men participated and 825 (65%) men took part in both dietary and medical examinations. These examinations were repeated in 1990, 1995 and 2000.

Baseline data was collected in 1960 before the Helsinki Declaration was developed, and oral informed consent was obtained in view of follow-up data. In 1985 and 1990, the study was approved by the Medical Ethics Committee of the University of Leiden, The Netherlands,

and in 1995 and 2000, by the Medical Ethics Committee of the Netherlands Organisation for Applied Scientific Research (TNO).

Assessment of smoking habits

Information on smoking habits was collected using standardized questionnaires. From 1960 until 1990 detailed information was gathered on type and amount of smoking (cigarette, cigar and pipe). The 1995 and 2000 questionnaires combined cigar and pipe smoking, and participants were asked whether they still smoked and how much they smoked per day. In 1960 and 1985, information on the age at smoking initiation and, in case of former smokers, age at cessation was collected for cigarette smoking. Duration of cigarette smoking was calculated using information on duration of smoking at baseline and information on smoking in the following measurement years. In addition, we calculated time until death or censoring since smoking cessation. As the number of men who smoked a pipe was small, men who smoked cigar, pipe or both were considered as one group. Additionally, we created an overall smoking variable, combining cigarette and cigar or pipe smoking. The present study has a relatively small sample size and the number of never smokers is very small. Consequently, for cigarette, cigar or pipe and overall smoking, men were divided into categories of never or long-term ex-smokers –that is, stopped smoking ≥10 years ago, recent ex-smokers –that is, stopped smoking <10 years ago, and current smokers. At the start of this study, the number of current smokers was very high and decreased remarkably during 40 years of follow-up. As similar trends in smoking habits were seen in the general Dutch population, the information on smoking habits was considered valid.

Assessment of potential confounders

Information on food consumption was collected using the cross-check dietary history method, adapted to the Dutch situation (17;18). Energy and alcohol intake was calculated using food composition tables close to the year of measurement. The participants were divided into two groups according to alcohol use (yes or no). Alcohol use was defined as having at least 1 g of alcohol intake per day, which is equivalent to about one alcoholic beverage per week.

During medical examinations, the weight and height of men were measured and body mass index (BMI) was calculated (kg/m^2). Information about the prevalence and history of myocardial infarction (MI), stroke, diabetes mellitus (DM) and cancer was collected throughout the study. The men were classified into four levels of socioeconomic status (manual workers, non-manual workers, small business owners and professionals) according to occupation at baseline.

Case assessment

Participants were followed until death, or censoring on 30 June 2000. During the study, six participants were lost to follow-up and were censored after their last physical examination. The final causes of death were ascertained by one clinical epidemiologist and coded according to the International Classification of Diseases, Eighth Revision (codes 410.0-414.9 for coronary heart disease, codes 390.0-459.9 for CVD, codes 140.0-208.9 for cancer, codes 162.0-162.9 for lung cancer and codes 490.0-492.9 and 496 for COPD). Because the underlying cause of death in elderly people is often difficult to ascertain, we included primary, secondary and tertiary causes of death in our analyses.

Statistical analysis

Cox proportional hazard analyses were performed with age as the time variable, with smoking information updated at each measurement round. In addition, we modelled the effects of duration of cigarette smoking (per 10 years), the number of cigarettes smoked (per 10 cigarettes per day) and time since cigarette smoking cessation (per 5 years) both separately as well as combined (8). As many smokers quit at the time of serious illness, the number of cigarettes smoked was adjusted for ever smoking (yes or no). The duration of smoking and the time since cigarette smoking cessation were adjusted for age at initiation.

We determined differences in life expectancies at age 40 and the number of disease-free years of life between current smokers and never or long-term ex-smokers, by calculating the area under survival curves. For disease-free years of life, survival until the age of onset of either MI, stroke, DM or cancer was used. Smokers who stopped smoking during follow-up were excluded from the analyses from the moment they stopped, and men who started smoking during follow-up were included in the analyses from the moment they started. The differences in life expectancy and the number of disease-free years of life due to cigar or pipe smoking were studied among men who were never or long-term ex-cigarette smokers. In addition, we calculated differences in life expectancy and the number of disease-free years of life for different ages at cigarette smoking cessation (age 40, 50, 60 or 70 years) compared with continuing smoking at that age and for every 10 cigarettes per day increase. A Cox proportional hazard model, with age as the time variable, was used to obtain the survival curves, adjusted for baseline covariates. For those men who started the study in 1960, values in 1960 were used as baseline values, whereas, for those men who started the study in 1985, values in 1985 were used as baseline values. 95% CIs were obtained using the bootstrap method (19).

For Cox proportional hazard models, the PHREG procedure of SAS/STAT software V.9.1 was used. The covariates in multivariate models included energy intake (kcal/day), use of alcohol (yes/no), BMI (kg/m^2) and baseline socioeconomic status (manual workers, non-manual workers, small business owners and professionals), and were updated at each measurement round. We adjusted for the prevalence of MI (yes/no), stroke (yes/no), DM (yes/no) and cancer (yes/no), updating this information at each measurement round, to account for the possibility that smokers quit smoking because of serious illness. Furthermore, cigarette smoking was adjusted for cigar or pipe smoking. All available data was used for the analysis.

Results

Table 2.1 shows the major characteristics of the men participating in the Zutphen Study during 40 years of follow-up (mean follow-up of all participants: 28 years). During follow-up, 1130 of the 1373 men died: CVD was the primary cause of death in 36% of all deaths, and coronary heart disease in 20% of all deaths. Total cancer, lung cancer and COPD were the primary cause in respectively, 26%, 10% and 4% of all deaths. Of the men who were included in the study in 1960, 74% smoked cigarettes in 1960. Among those men who were still alive in 2000, 12% were current cigarettes smokers (**figure 2.1A**). The percentage of current smokers was lower among the men who were newly included in 1985. Moreover, the current smokers in 1960 had an average cigarette smoking duration of 17 years during 40 years of follow-up. For the current smokers in 1985, this figure was 7 years. Among smokers, the number of cigarettes smoked per day decreased from 13 to 3 cigarettes in the period 1960-2000.

Table 2.1. Characteristics of men participating in the Zutphen Study by year of measurement

	Cohort	1960	1965	1970	1985	1990	1995	2000
Number of participants	*1960*	872	721	615	349	231	114	51
	1985	-	-	-	476	306	161	68
Cumulative number of deaths	*1960*	-	48	109	429	561	670	766
	1985	-	-	-	-	97	232	364
Age (years)		49 ± 6	54 ± 5	59 ± 5	71 ± 5	75 ± 5	80 ± 4	83 ± 3
Overall smoking (%)								
Never and long-term ex[1]		6	6	9	26	50	60	72
Recent ex[2]		6	11	15	31	17	16	14
Cigarettes, cigars or pipes		52	35	25	7	4	2	0
Cigarettes		23	26	29	23	19	16	6
Cigars or pipes		14	21	23	13	10	6	8
Duration of cigarette smoking	*1960*	29 ± 11	34 ± 14	34 ± 14	39 ± 18	40 ± 19	42 ± 20	37 ± 21
(years)[3]	*1985*	-	-	-	33 ± 21	32 ± 22	29 ± 22	28 ± 20
Energy without alcohol (kcal)		3082 ± 673	2921 ± 673	2539 ± 539	2147 ± 507	2029 ± 459	2033 ± 469	1992 ± 457
Alcohol (percentage users)		36	59	69	70	66	68	75
BMI (kg/m2)		24.1 ± 2.7	24.9 ± 2.7	25.2 ± 2.8	25.5 ± 3.1	25.5 ± 3.2	25.3 ± 3.4	26.0 ± 3.3

Values are represented as mean ± SD, unless indicated otherwise; [1]Never and long-term ex-smokers are defined as men who never smoked or stopped smoking ≥10 years ago; [2]Recent ex-smokers are defined as men who stopped smoking <10 years ago; [3]Mean duration of cigarette smoking includes the men who never smoked (duration=0).

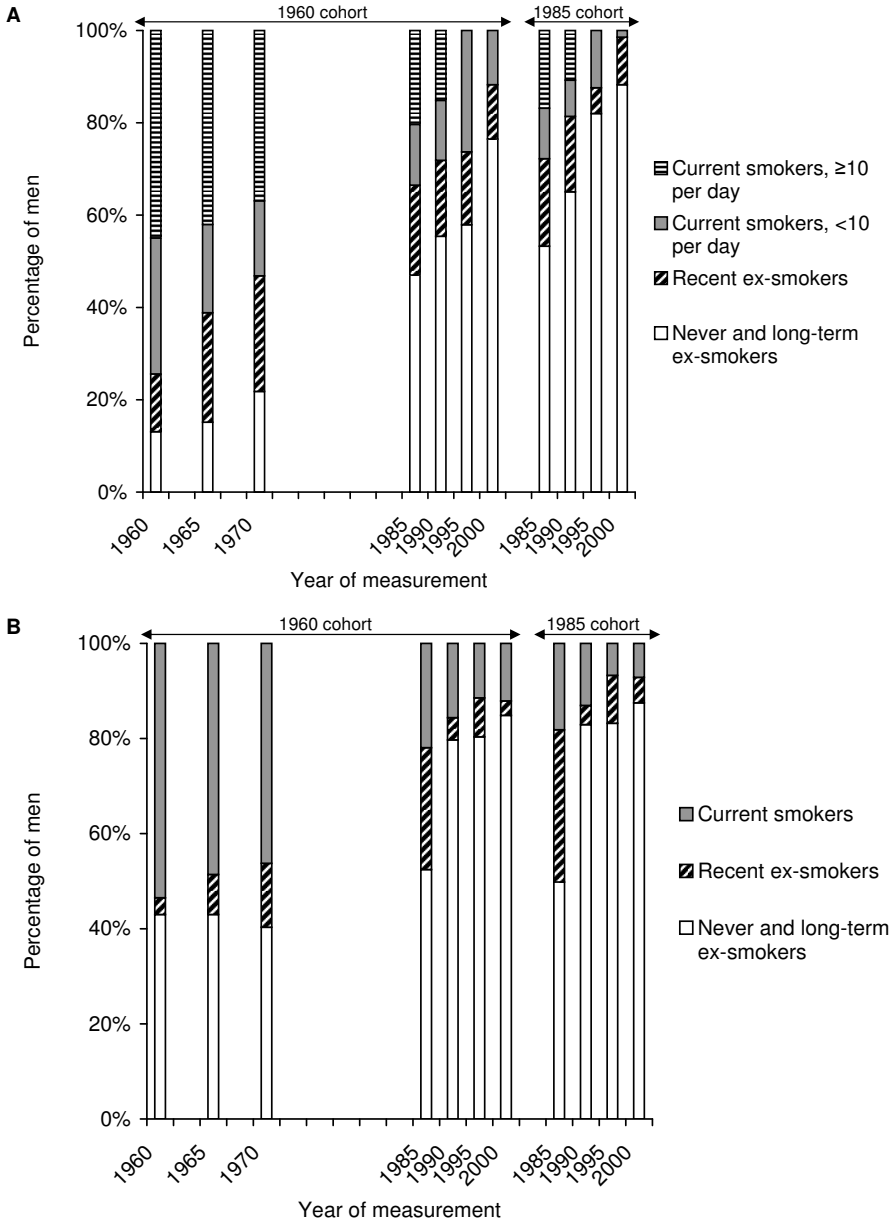

Figure 2.1. Changes in cigarette (A) and exclusive cigar or pipe (B) smoking within the Zutphen Study, during 40 years of follow-up. Changes in exclusive cigar or pipe smoking were studied among those men who were never or long-term ex-cigarette smokers. Recent ex-smokers are defined as men who stopped smoking <10 years ago. Never and long-term ex-smokers are defined as men who never smoked or stopped smoking ≥10 years ago.

In 1960, the percentage of cigar or pipe smoker among those men who were never or long-term ex-cigarette smokers was 54% (**figure 2.1B**). These exclusive cigar or pipe smokers smoked, on average, three cigars and six pipes per day. Again, the percentage of exclusive cigar or pipe smokers was lower among men who were newly included in 1985. The percentage of alcohol users doubled from 36% in 1960 to 75% in the period 1985-2000. Average energy intake, without alcohol, decreased substantially from 3082 to 1992 kcal/day. Average BMI increased from 24.1 kg/m^2 in 1960 to 26.0 kg/m^2 in 2000.

Using updated information at each measurement round and after adjustment for potential confounders, smoking was strongly associated with all-cause and cause-specific mortality (**table 2.2**). Hazard ratios (HR) for current cigarette smoking varied between 1.40 (95% CI: 1.07 to 1.83) for cancer mortality and 2.90 (1.80 to 4.68) for COPD mortality. The associations between recent ex-smoking and mortality were weaker, and varied between 1.15 (0.84 to 1.57) and 2.98 (1.78 to 5.01) for cancer and COPD mortality, respectively. In general, the associations between smoking and mortality were stronger for overall smoking compared with cigarette smoking. Furthermore, for cardiovascular mortality we found a significant and inverse interaction between smoking status and survival age. This indicates that the association between smoking status and cardiovascular mortality weakens with a higher survival age.

Every 10-year increase in cigarette smoking duration was strongly associated with mortality from all-causes (HR: 1.12), CVD (HR: 1.15), lung cancer (HR at mean survival age: 1.31) and COPD (HR: 1.38), independent of the number of cigarettes smoked (**table 2.3**). In addition, every 10 cigarettes per day increase was associated with all-cause mortality (HR: 1.11), independent of smoking duration (table 2.3). When studying the association between duration of cigarette smoking and lung cancer mortality, we found a significant and inverse interaction with survival age. This indicates that the association between duration of cigarette smoking and mortality weakens with a higher survival age.

Moreover, omitting the adjustment for the prevalence of chronic diseases attenuated our results slightly but the overall conclusions remained the same, except for cancer mortality. For total cancer mortality, the HR for every 10 cigarettes per day increase increased from 1.14 (0.97 to 1.32) to 1.24 (1.06 to 1.43) and the HR for every 10-year increase in cigarette smoking duration increased from 1.07 (0.96 to 1.19) to 1.11 (1.01 to 1.22), whereas for lung cancer mortality these HR changed from 1.14 (0.90 to 1.44) to 1.32 (1.11 to 1.58) and from 1.31 (1.07 to 1.60) to 1.25 (1.06 to 1.47), respectively. As duration of smoking and time since cessation were strongly and inversely correlated (Rho $\leq$-0.78), we were not able to include both in the same model. The separate associations of time since cigarette smoking cessation with mortality were opposite to the association for smoking duration (data not shown). Age at initiation of cigarette smoking did not independently contribute to mortality risk and was therefore left out of the models.

Table 2.2. Smoking in relation to mortality[1] within the Zutphen Study, according to updated covariates at each measurement round

		Overall smoking		Cigarette smoking	
	Smoking state	**Crude HR (95% CI)**	**Adjusted HR (95% CI)[2]**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)[2]**
All cause	Recent ex-smoker[3]	1.57 (1.31 to 1.89)	1.47 (1.21 to 1.77)	1.51 (1.28 to 1.78)	1.39 (1.17 to 1.65)
	Current smoker	1.78 (1.53 to 2.08)	1.69 (1.44 to 1.99)	1.70 (1.48 to 1.96)	1.60 (1.38 to 1.86)
Total cardiovascular	Recent ex-smoker	1.40 (1.09 to 1.80)	1.51 (1.15 to 1.99)[4]	1.41 (1.12 to 1.76)	1.38 (1.09 to 1.74)
	Current smoker	1.55 (1.26 to 1.91)	1.78 (1.41 to 2.24)[4]	1.56 (1.29 to 1.89)	1.66 (1.35 to 2.03)
Coronary heart disease	Recent ex-smoker	1.37 (0.96 to 1.95)	1.27 (0.89 to 1.83)	1.42 (1.04 to 1.95)	1.33 (0.96 to 1.85)
	Current smoker	1.35 (1.01 to 1.82)	1.54 (1.13 to 2.10)	1.41 (1.07 to 1.86)	1.59 (1.18 to 2.13)
Total cancer	Recent ex-smoker	1.74 (1.24 to 2.44)	1.28 (0.91 to 1.82)	1.54 (1.15 to 2.08)	1.15 (0.84 to 1.57)
	Current smoker	1.93 (1.45 to 2.57)	1.51 (1.11 to 2.05)	1.81 (1.40 to 2.33)	1.40 (1.07 to 1.83)
Lung cancer	Recent ex-smoker	2.80 (1.44 to 5.44)	2.00 (1.02 to 3.92)	2.29 (1.35 to 3.88)	1.72 (1.00 to 2.95)
	Current smoker	3.86 (2.17 to 6.87)	2.93 (1.60 to 5.35)	3.25 (2.08 to 5.08)	2.34 (1.47 to 3.75)
COPD	Recent ex-smoker	2.15 (1.21 to 3.85)	2.29 (1.27 to 4.13)	2.96 (1.78 to 4.92)	2.98 (1.78 to 5.01)
	Current smoker	2.43 (1.48 to 4.00)	2.23 (1.32 to 3.76)	3.30 (2.09 to 5.21)	2.90 (1.80 to 4.68)

COPD, chronic obstructive pulmonary disease; [1]Because of missing data, the number of events may be smaller than the number mentioned in table 2.1; [2]Hazard ratio adjusted for energy intake, alcohol use, body mass index, baseline socioeconomic status, prevalence of myocardial infarction, stroke, diabetes mellitus and cancer. Cigarette smoking is additionally adjusted for cigar or pipe smoking; [3]Recent ex-smokers are defined as men who stopped smoking <10 years ago; [4]Hazard ratios were calculated using mean survival age (76 years).

Table 2.3. Modelling cigarette smoking history in relation to mortality[1] within the Zutphen Study, according to updated covariates at each measurement round

	Crude HR (95% CI)[2]	**Adjusted HR (95% CI)**[3]	**Adjusted HR (95% CI)**[4]
All cause			
No of cigarettes smoked (per 10 cigarettes/ day)	1.22 (1.13 to 1.32)	1.10 (1.00 to 1.20)	1.11 (1.01 to 1.21)
Duration (per 10 years)	1.11 (1.08 to 1.14)	1.13 (1.07 to 1.18)	1.12 (1.06 to 1.18)
Total cardiovascular			
No of cigarettes smoked (per 10 cigarettes/ day)	1.11 (1.00 to 1.24)	0.99 (0.88 to 1.13)	1.06 (0.93 to 1.20)
Duration (per 10 years)	1.09 (1.04 to 1.13)	1.13 (1.06 to 1.21)	1.15 (1.07 to 1.23)
Coronary heart disease			
No of cigarettes smoked (per 10 cigarettes/ day)	1.12 (0.97 to 1.30)	1.05 (0.88 to 1.25)	1.17 (0.98 to 1.39)
Duration (per 10 years)	1.07 (1.01 to 1.14)	1.08 (0.98 to 1.20)	1.10 (1.00 to 1.21)
Total cancer			
No of cigarettes smoked (per 10 cigarettes/ day)	1.36 (1.20 to 1.54)	1.25 (1.08 to 1.45)	1.14 (0.97 to 1.32)
Duration (per 10 years)	1.17 (1.10 to 1.24)	1.12 (1.02 to 1.22)	1.07 (0.96 to 1.19)
Lung cancer			
No of cigarettes smoked (per 10 cigarettes/ day)	1.65 (1.38 to 1.98)	1.36 (1.10 to 1.70)	1.14 (0.90 to 1.44)
Duration (per 10 years)	1.42 (1.26 to 1.61)	1.29 (1.09 to 1.52)	1.31 (1.07 to 1.60)[5]
COPD			
No of cigarettes smoked (per 10 cigarettes/ day)	1.18 (0.95 to 1.48)	0.81 (0.62 to 1.07)	0.99 (0.73 to 1.33)[5]
Duration (per 10 years)	1.34 (1.20 to 1.49)	1.51 (1.28 to 1.78)	1.38 (1.17 to 1.63)

COPD, chronic obstructive pulmonary disease; [1]Because of missing data, the number of events may be smaller than the number mentioned in table 2.1; [2]Crude HR, hazard ratio for separate models for duration and the number of cigarettes (adjusted for ever smoking (yes/no)); [3]HR for multivariate models including duration of cigarette smoking and the number of cigarettes smoked, adjusted for ever smoking; [4]HR for multivariate models with additional adjustment for cigar or pipe smoking, energy intake, alcohol use, body mass index, baseline socioeconomic status and the prevalence of myocardial infarction, stroke, diabetes mellitus and cancer; [5]Hazard ratios were calculated using mean survival age (76 years).

Figure 2.2 shows the adjusted survival curve used for determining the life expectancies at age 40. Current cigarette smoking reduced life expectancy by 6.8 years and the number of disease-free life years-that is, years free from MI, stroke, DM and cancer-by 5.8 years. For current overall smoking, the adjusted difference in life expectancy between smokers and never or long-term ex-smokers was comparable to cigarette smoking (**table 2.4**). Among the exclusive cigar or pipe smokers, life expectancy was reduced by 4.7 (1.5 to 8.0) years and the number of disease-free years of life by 3.7 (-1.7 to 9.1) years. After adjustment for potential confounders, the total number of life-years lost due to cigar or pipe smoking was 4.7 (1.4 to 8.0) years and the number of disease-free life-years lost was 5.2 (-1.5 to 12.0) years. In addition, the number of total and disease-free years of life lost increased when more cigarettes were smoked (table 2.4). The adjusted number of total life-years lost ranged from 2.1 for men who smoked 11-

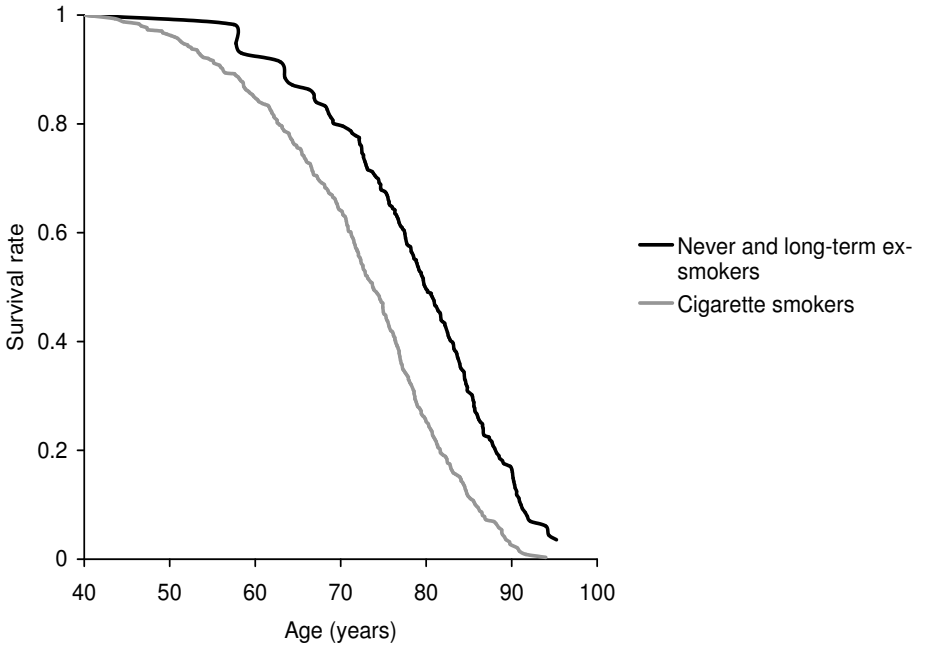

Figure 2.2. Survival curves for cigarette smokers and never and long-term ex-smokers within the Zutphen Study, adjusted for baseline energy intake, alcohol use, body mass index, prevalence of myocardial infarction, stroke, diabetes mellitus and cancer, socioeconomic status, and cigar or pipe smoking.

20 cigarettes per day to 8.8 years for men who smoked >30 cigarettes per day, whereas the number of disease-free life-years lost ranged from 2.1 years to about 10.6 years. Men who stopped smoking at age 40 gained 4.6 life-years, compared with men who continued smoking at that age (table 2.4), while the gained life-years were 2.5-3.3 years among men who stopped smoking at age 50, 60 or 70 years. The number of disease-free years of life gained by stopping smoking after age 40 were less compared with the total number of life-years gained, but still 0.3-3.0 years.

Discussion

Our results clearly show the importance of amount, duration and type of smoking in the relation to mortality. Average cigarette smoking reduced life expectancy at age 40 by about 7 years and heavy cigarette smoking reduced life expectancy even more. The average cigar or pipe smoker lost about 5 life-years. Smoking decrease total life expectancy, and also decreased the number of disease-free years of life, but to a smaller extent. Moreover, stopping cigarette smoking at age 40 increased the total life expectancy by about 5 years and the number of disease-free years of life by about 3 years.

The major strength of this study was the collection of detailed information on smoking habits at each of seven examination rounds during 40 years of follow-up. This enabled us to study long-term effects of cigarette as well as cigar or pipe smoking on mortality and life expectancy. Moreover, detailed data on potential confounders made it possible to study the

Table 2.4. Differences in life expectancy (in years) due to smoking within the Zutphen Study, crude and adjusted for potential confounders

		Total life expectancy		Disease-free years of life	
		Crude difference (95% CI)	**Adjusted difference (95% CI)[1]**	**Crude difference (95% CI)**	**Adjusted difference (95% CI)[1]**
Current overall smoking[2]		-6.8 (-9.1 to -4.5)	-6.5 (-11.5 to -1.4)	-5.8 (-8.5 to -3.1)	-5.9 (-8.6 to -3.1)
Current cigarette smoking[2]		-7.5 (-10.1 to -4.9)	-6.8 (-9.3 to -4.3)	-5.9 (-8.8 to -3.0)	-5.8 (-8.6 to -2.9)
No. of cigarettes	1-10	-4.3 (-7.0 to -1.6)	-4.3 (-7.1 to -1.4)	-2.8 (-5.6 to 0.1)	-2.9 (-5.9 to 0.0)
Smoked[1]	11-20	-2.3 (-4.0 to -0.5)	-2.1 (-4.1 to -0.2)	-2.1 (-4.7 to 0.5)	-2.1 (-4.6 to 0.3)
	21-30	-5.7 (-8.5 to -2.8)	-5.8 (-8.6 to -2.9)	-8.1 (-11.3 to -4.9)	-8.2 (-11.3 to -5.0)
	>30	-8.9 (-14.0 to -3.8)	-8.8 (-13.9 to -3.7)	-11.0 (-16.2 to -5.7)	-10.6 (-14.9 to -6.3)
Stopped at age (years)[3]	40	5.5 (3.3 to 7.6)	4.6 (2.3 to 6.8)	3.6 (0.9 to 6.4)	3.0 (0.4 to 5.6)
	50	3.8 (2.3 to 5.4)	3.3 (1.9 to 4.7)	2.6 (0.7 to 4.5)	1.7 (-0.2 to 3.5)
	60	3.3 (2.2 to 4.4)	2.8 (1.7 to 4.0)	1.2 (-0.2 to 2.7)	0.7 (-0.9 to 2.3)
	70	2.6 (1.8 to 3.4)	2.5 (1.6 to 3.4)	0.5 (-1.1 to 2.0)	0.3 (-1.3 to 1.9)

[1]Difference adjusted for baseline energy intake, alcohol use, body mass index, prevalence of myocardial infarction, stroke, diabetes mellitus and cancer, and socioeconomic status. Current cigarette smoking was additionally adjusted for cigar or pipe smoking; [2]The number of life-years lost compared to never or long-term ex-smokers that is, men who stopped smoking $\geq$10 years ago; [3]The differences represent the number of life-years lost compared with continuing smoking at that age.

independent effect of smoking. Adjustment for potential confounders reduced the number of life-years lost by half a year.

This study also has weaknesses. Firstly, the Zutphen Study had a relatively small study population which may have led to less precise results. Secondly, the number of never smokers was also very small, and we were therefore forced to combine men who stopped smoking for ≥10 years with men who never smoked in our reference group. Because studies have suggested that mortality risk after 10 years of smoking cessation is comparable to that of in never-smokers (2;20), we used this cut-off value. However, more recent studies showed that mortality risk is comparable to that in never-smokers only after 10-15 (21-24) or more (24-26) years of cessation and so the differences in life expectancy may have been underestimated. Thirdly, the Zutphen Study started in 1960 with 872 men. The cohort of men who survived until 1985 was expanded with an additional cohort of 559 men. However, since this additional cohort of men was from the same birth cohort as the men who started the study in 1960, it is unlikely that bias was introduced.

Our findings confirmed results from others that also showed an increase in all-cause mortality risk with cigarette smoking duration and the number of cigarettes smoked (9;13-15;20;23;27-30). After the adjustment for the prevalence of MI, stroke, DM and cancer, only cigarette smoking duration was associated with lung cancer mortality. By omitting this adjustment for chronic disease prevalence, both smoking duration as well as the number of cigarette smoked were found to be strongly associated with total cancer and lung cancer mortality. This result confirms those from other studies (9-11;15;20;28-30). In addition, we confirmed the results of other studies which showed dose-response relationships between smoking duration and COPD mortality (9;15).

In accordance with other studies (6;7), the effects of cigar or pipe smoking on mortality were weaker compared to the effects of cigarette smoking. To our knowledge, we are the first to reported on the effects of exclusive cigar or pipe smoking on life expectancy. This study found that the effects on life expectancy observed for cigar or pipe smoking were close to those observed for cigarette smoking. Exclusive cigar or pipe smoking reduced life expectancy by about 5 years, whereas cigarette smoking reduced life expectancy by about 7 years.

In the British Doctors Study (4), the Framingham Heart Study (31) and the Cancer Prevention Study II (32), the reduction in life expectancy due to smoking was about 9 years. The difference in the reduction in life expectancy compared with this study may be due to several factors. Firstly, life expectancy within these studies was assessed at different ages. Secondly, men who stopped smoking ≥10 years ago were not included in the reference group. Thirdly, the adjustment for possible confounders was not carried out in these studies and, finally, the average amount smoked might have been higher compared with that in this study. Both the British Doctors Study (29) as well as our study found that heavy cigarette smokers lost 9-10 life-years, indicating that the amount smoked is associated with reductions in life expectancy.

In accordance with the British Doctors Study (4) and the Cancer Prevention Study II (32), we found that smoking cessation has beneficial effects on life expectancy. These studies as well as this study found a substantial increase in life expectancy of about 3 years when stopping smoking at age 60. The main focus in smoking prevention programmes is preventing smoking initiation. The results from this and other studies indicate that the persuasion of smokers to quit smoking, even later in life, should be another important focus from a public health perspective.

In this study, the reduction in the number of disease-free years of life due to smoking was comparable between the different types of smoking. Other studies also addressed the differences in the number of disease-free years of life (31;33;34). Although these studies defined disease-free years of life differently from this study and did not distinguish between different types of smoking, the overall conclusions were similar. Never smokers and quitters live longer than continuing smokers, and they also spend more years of life in better health.

In summary, cigarette and cigar or pipe smoking reduces life expectancy and the number of disease-free years of life. However, the number of life-years lost due to cigar or pipe smoking is fewer compared with cigarette smoking. Both the number of cigarettes smoked and smoking duration are strongly associated with mortality risk and the number of life-years lost. Although our results indicate that the effects will be larger the earlier one quits, even stopping at age 60 has major benefits on life expectancy.

Conflict of interest: None.

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Chapter 3

Long-term wine consumption is independently of moderate alcohol intake related to cardiovascular mortality and life expectancy: The Zutphen Study

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Abstract

Background: Light to moderate alcohol intake lowers the risk of cardiovascular mortality, but whether this protective effect can be attributed to a specific type of beverage remains unclear. Moreover, little is known about the effects of long-term alcohol intake on life expectancy.

Methods: The impact of long-term alcohol intake and types of alcoholic beverages consumed on cardiovascular mortality and life expectancy at age 50 was investigated in the Zutphen Study, a cohort of 1373 men born between 1900 and 1920, and examined repeatedly between 1960 and 2000. Hazard ratios for total alcohol intake and alcohol from wine, beer and spirits were obtained from time-dependent Cox regression models. Life expectancy at age 50 was calculated from areas under survival curves.

Results: Long-term light alcohol intake, i.e. ≤20 grams per day, compared to no alcohol, was strongly and inversely associated with cerebrovascular (HR: 0.43 [0.26 to 0.70]), total cardiovascular (HR: 0.70 [0.55 to 0.89]) and all-cause mortality (HR: 0.75 [0.63 to 0.91]). Independent of total alcohol intake, long-term wine consumption of, on average, less than half a glass per day was strongly and inversely associated with coronary heart disease (HR: 0.61 [0.41 to 0.89]), total cardiovascular (HR: 0.68 [0.53 to 0.86]) and all-cause mortality (HR: 0.73 [0.62 to 0.87]). These results could not be explained by differences in socioeconomic status. Life expectancy was about 5 years longer in men who consumed wine compared to those who did not use alcoholic beverages.

Conclusion: Long-term light alcohol intake lowered cardiovascular and all-cause mortality risk, and increased life expectancy. Light wine consumption was associated with a 5 years longer life expectancy; however, more studies are needed to verify this result.

Introduction

Many studies have demonstrated a U- or J-shaped relationship between alcohol intake and all-cause mortality. This association can be explained by a lower risk of cardiovascular disease (CVD) mortality in light to moderate drinkers (1-4). The protective effect of light to moderate alcohol intake may be due to an increase in HDL cholesterol and prevention of blood clotting and reduction of platelet aggregation (5;6). Red wine consumption may have an additional health benefit because of its polyphenolic compounds (7;8) that interfere with the initiation, progression and rupture of atherosclerotic plaques (9), and improve endothelial function (10;11). Although some epidemiological studies showed beneficial effects of wine consumption (12;13), results of several other studies do not show an advantage of one type of alcoholic beverage over another (14). Studies have suggested that the beneficial effects of wine consumption compared to other beverages can mainly be attributed to differences in socioeconomic status, dietary and other lifestyle habits (15;16).

In prospective cohort studies in which alcohol intake is only assessed at the baseline examination, consumption patterns are assumed to be relatively constant over the entire study period. However, it is unlikely that exposure measurements in the past accurately reflect long-term alcohol intake since consumption patterns usually change during life. To get correct estimates of long-term effects of alcohol intake, repeated measures are needed. Moreover, the use of repeated measures, especially when using a cumulative average method, reduces within-subject variation over time and, thereby, misclassification in alcohol intake (17).

In epidemiological studies, hazard ratios are commonly used to express the impact on mortality. Since hazard ratios express effects for an exposed group relative to the effect of the unexposed group, they do not provide information regarding absolute health effects. Such insight can be obtained by the calculation of life expectancies and the number of life-years lost. Although concepts like life expectancy are more informative and easier to understand, they are not reported frequently.

The objective of the present study is to assess the relationship between long-term intake of alcohol and the types of alcoholic beverages consumed, and cardiovascular and all-cause mortality. To obtain more accurate effect estimates, we used seven repeated measures of the consumption of alcoholic beverages. In addition to hazard ratios, we present our results also in terms of differences in life expectancy.

Methods

Study population

The Zutphen Study has been carried out since 1960 among middle-aged men in Zutphen, an old industrial town in the eastern part of the Netherlands with about 30 000 inhabitants. In 1960, a random sample was drawn of 1088 men born between 1900 and 1919 and residing for at least 5 years in Zutphen. Of those men, 878 participated in the Zutphen Study (response rate: 81%). Examinations were repeated in 1965, 1970, 1985, 1990, 1995 and 2000. In 1985, the group of 554 survivors was extended with a new random sample of men of the same age. Of the 1266 men who were invited in 1985, 939 men participated (response rate: 74%). In every examination round, the participants that took part in both the dietary and physical examinations were selected for the present study (1373 men).

Baseline data were collected in 1960 before the Helsinki Declaration was developed and oral informed consent was obtained in view of follow-up data. In 1985 and 1990, the study was approved by the Medical Ethics Committee of the University of Leiden, The Netherlands, and in 1995 and 2000, by the Medical Ethics Committee of the Netherlands Organisation for Applied Scientific Research (TNO).

Assessment of alcohol and food consumption

The habitual alcohol consumption was assessed as part of the total diet, using the cross-check dietary history method (18), adapted to the Dutch situation (19;20). This method provides information about the participant's usual food and alcohol consumption pattern, 6 to 12 months preceding the interview. From 1985 onwards, the information about the usual food and alcohol consumption pattern was limited to the month preceding the interview because consumption patterns from 1985 were much more complicated than those in the 1960s. The daily intake of alcohol, energy and other nutrients was calculated using food composition tables close to the year of measurement (21-23). Alcohol intake was highly reproducible (r=0.8) (24) and ranking of the participants was considered valid as shown by the strong correlation with HDL cholesterol (25).

To assess the relationship between different types of alcoholic beverages and mortality, we calculated the alcohol intake from wine, beer or spirits, respectively. Participants were grouped into three categories according to their intake of total alcohol and of alcohol from beer, wine or spirits: 0, >0-20, and >20 g/d. Since studies have suggested that using non-drinkers as a reference group is unsuitable for studying the effects of alcohol on mortality because of the higher background risk among the former drinkers (26-28), we created a time-dependent indicator variable for those men who stopped drinking during follow-up.

Assessment of potential confounders

Detailed information on type and amount of smoking was collected using standardized questionnaires. Cigarette, cigar or pipe smokers were divided into categories of never or long-term ex-smokers, i.e. stopped smoking ≥10 years ago, recent ex-smokers, i.e. stopped smoking <10 years ago, and current smokers. Also, the number of years of cigarette smoking was calculated. During physical examinations men's weight and height were measured and body mass index (BMI) was calculated. Information about the prevalence and history of clinical myocardial infarction (MI), stroke, diabetes mellitus (DM), and cancer was collected throughout the study. The men were classified into four levels of socioeconomic status (manual workers, non-manual workers, small business owners and professionals) according to occupation at baseline.

Case ascertainment

Participants were followed until death, or censored on June 30, 2000. Three participants were lost to follow-up during the study and were censored after their last physical examination. Information about the causes of death was available from the official death certificate, the medical history collected from interviewing physicians or relatives of the dead person and other witnesses, and from abstracts of hospital and other medical records (29). The adjudication of the underlying causes of death were done by one clinical epidemiologist (Dr Alessandro Menotti,

Association for Cardiac Research, Rome, Italy) and coded according to the International Classification of Diseases; Eight Revision (codes 410 to 414 for coronary heart disease [CHD], codes 430 to 438 for cerebrovascular diseases and codes 390 to 458 for CVD) (30). Because the underlying cause of death in elderly people is often difficult to ascertain, we included primary and secondary causes of cardiovascular death.

Statistical analysis

Cox proportional hazard analyses with age as the time variable (31;32) were performed using the PHREG procedure of SAS/STAT software (version 9.1; SAS Institute, Inc, Cary, NC). Time at entry was age on December 31st of the year preceding the year the men participated in both the dietary and physical examinations for the first time, i.e. the first measurement round; exit time was age at death, age when lost to follow-up, or age when censored, whichever came first. We calculated the cumulative average alcohol intake to better represent long-term intake. With this method, exposure between 1960 and 1965 was calculated from the alcohol intake from the 1960 examination round; exposure between 1965 and 1970 was calculated from the average alcohol intake from the 1960 and 1965 examination rounds, and so on (17). For those men who were newly included in the study in 1985, information on alcohol intake was missing in the period 1960-1970. To take into account that average alcohol intake was higher in 1985 than in 1960-1970 and that taking cumulative averages excluding earlier intakes in those men who were newly in the study in 1985 would overestimate their intake compared to men included in 1960, multiple imputation (33), five times, of alcohol intake and dietary covariates between 1960 and 1970 was carried out with an adapted version of predicted mean matching (34). The SAS code that was used for the multiple imputation can be downloaded from www.rivm.nl/sasmacros. Analyses on long-term alcohol intake were performed on five imputed datasets and results were pooled using the MIANALYZE procedure of SAS/STAT software.

The covariates in the multivariable models included an indicator variable for former drinker, energy intake without alcohol (kcal/d), consumption of vegetables (g/d), fruit (g/d) and fish (g/d), intake of saturated and *trans* fatty acids (g/d), BMI (kg/m2), cigar or pipe smoking (never and long-term ex, recent-ex and current), cigarette smoking duration (divided by 10 years), the daily number of cigarettes smoked (divided by 10), prevalence of MI (yes or no), stroke (yes or no), DM (yes or no), and cancer (yes or no), and indicator variables for baseline socioeconomic status. In additional analyses, the multivariable models for, respectively, alcohol from beer, wine and spirits were additionally adjusted for total alcohol intake to investigate the independent effects of alcohol from one specified alcoholic beverage type. In the multivariable analyses, the cumulative average intake of all dietary covariates was calculated and non-dietary covariates were updated at each measurement round. To test the proportional hazards assumption, a product term between alcohol intake and age was included in the model, and a *P*-value for interaction <0.10 was considered statistically significant.

We determined differences in life expectancy at age 50, i.e. average age at baseline, between men with different levels of cumulative average alcohol intake, by calculating the area under survival curves (35). To distinguish between the effects of alcohol intake and the effects of alcoholic beverage types, we compared the life expectancies for men who consumed alcohol from wine (>0 gram per day) with those who consumed alcohol from beer and spirits and those who consumed no alcohol from the specified sources, using cumulative average

intake at each measurement round. The men were included in the analysis during the period that they met the requirements for the exposure categories concerned. Cox models, with age as the time variable and stratified by categories of amount (0, >0-20, >20 g/d) or source (no alcohol, alcohol from wine, alcohol from beer or spirits) of alcohol intake, were used to obtain the survival curves. The Cox models were adjusted for baseline covariates, i.e. dietary and smoking variables, BMI, prevalence of chronic diseases, i.e. MI, stroke, DM and cancer, and socioeconomic status. Since several participants used more than one type of alcoholic beverage in their usual diet and are, thereby, included in different exposure categories at the same time, the COVSANDWICH (AGGREGATE) statement was added to the PHREG procedure. Areas under the survival curves from the five imputed datasets were pooled (33) and ninety-five percent confidence intervals were obtained using the bootstrap method (36).

Results

Population characteristics

During 40 years of follow-up (mean survival age: 77 years), 1130 of the 1373 men participating in the present study died (**table 3.1**). Of these deaths, 628 were cardiovascular disease (CVD) deaths, 348 were coronary heart disease (CHD) deaths, and 139 were cerebrovascular deaths.

The percentage of alcohol users almost doubled from 45% in 1960 to 86% in 2000 (table 3.1). Among users, average alcohol consumption increased from 8 g/d in 1960 to 18 g/d among the survivors in 1985, after which it decreased to 14 g/d in 2000 (table 3.1). The percentage of wine users increased remarkably from 2% in 1960 till about 40% in 2000. This increase was observed in all levels of socioeconomic status. Among users, the average number of glasses consumed varied between a half and 1.5 glasses per day for wine, beer and spirits. With the exception of 1960, alcohol from spirits contributed the most to the total alcohol intake (**figure 3.1**). The correlation between alcohol from spirits and total alcohol intake varied between 0.67 and 0.86. For alcohol intake from wine and beer, the correlations were lower.

Alcohol consumption, alcoholic beverages and mortality

Long-term alcohol intake was significantly and inversely associated with mortality risk (**table 3.2**). Men with less than or equal to 20 grams of long-term, i.e. cumulative average, alcohol intake had a 57% lower cerebrovascular mortality risk, a 30% lower CVD mortality risk, and a 25% lower all-cause mortality risk compared to men with no alcohol intake. The associations for more than 20 grams of long-term alcohol intake per day were weaker than those for less than or equal to 20 grams of long-term alcohol intake per day.

In the next step, the independent effects of long-term alcohol intake from wine, beer and spirits on mortality were estimated. After additional adjustment for total alcohol intake, less than or equal to 20 grams of long-term alcohol intake from wine per day –compared to no alcohol intake from wine– was inversely associated with CHD (HR: 0.61 [95%CI: 0.41 to 0.89]), CVD (HR: 0.68 [0.53 to 0.86]) and all-cause mortality risk (HR: 0.73 [0.62 to 0.87]; **table 3.3**). In the models for CVD and all-cause mortality, less than or equal to 20 grams of long-term total alcohol intake remained inversely associated with mortality (HR CVD mortality: 0.76 [0.59 to 0.97]; HR all-cause mortality: 0.80 [0.67 to 0.97]).

Table 3.1. Characteristics of men participating in the Zutphen Study by year of measurement[1]

		Cohort	1960	1965	1970	1985	1990	1995	2000
No. of participants[2]		1960	872	721	615	349	231	114	51
		1985				476	306	161	68
Cum. no. of deaths	*All-cause*		-	40	103	412	645	889	1130
	Total cardiovascular		-	20	61	261	376	514	628
	Coronary heart disease		-	13	40	176	231	297	348
	Cerebrovascular		-	3	10	49	78	113	139
Age (years)[3]			49 ± 6	54 ± 5	59 ± 5	71 ± 5	75 ± 5	80 ± 4	83 ± 3
Body mass index (kg/m2)			24.1 ± 2.7	24.9 ± 2.7	25.2 ± 2.8	25.5 ± 3.1	25.5 ± 3.2	25.3 ± 3.4	26.0 ± 3.3
Overall smoking (%)[4]	*Never and long-term ex*		6	6	9	26	50	60	72
	Recent ex		6	11	15	31	17	16	14
	Cigarettes		74	61	53	30	23	18	6
	Cigars or pipes		14	21	23	13	10	6	8
Energy intake without alcohol (kcal)			3082 ± 673	2920 ± 674	2539 ± 539	2146 ± 506	2029 ± 458	2029 ± 468	1991 ± 457
Alcohol intake (g/d)[5]		1960	8 ±13	10 ± 13	12 ± 13	18 ± 19	14 ± 15	14 ± 14	13 ± 11
		1985	-	-	-	18 ± 17	14 ± 14	13 ± 15	14 ± 16
Alcohol users (%)		1960	45	62	72	75	78	80	86
		1985	-	-	-	75	72	78	85
Beer users (%)		1960	38	35	42	24	22	22	37
		1985	-	-	-	24	25	25	29
Wine users (%)		1960	2	5	6	20	26	29	39
		1985	-	-	-	25	31	38	47
Spirits users (%)		1960	15	42	52	55	55	58	61
		1985	-	-	-	55	49	49	54

[1]Numbers represent means ± standard deviation, unless indicated otherwise; [2]In every measurement round, the participants that took part in both physical and dietary examinations were selected for the analyses; [3]Age is defined as age on December 31st of the year preceding the examination; [4]Never and long-term ex-smokers are defined as men who never smoked or stopped smoking ≥10 years ago; recent ex-smokers are defined as men who stopped smoking <10 years ago; [5]Average alcohol intake was calculated among alcohol users.

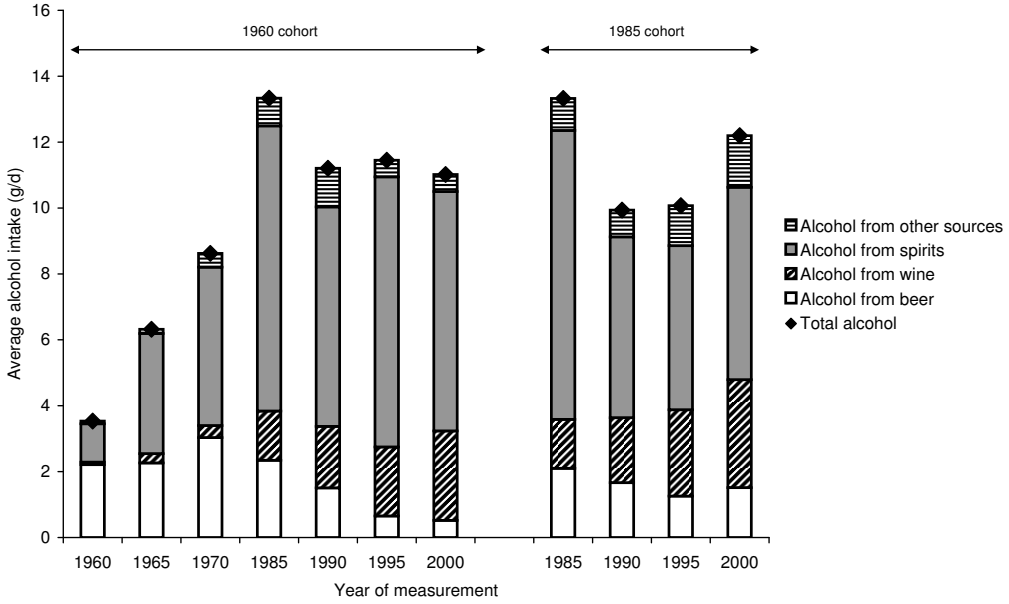

Figure 3.1. The contribution of alcohol from beer, wine and spirits to total alcohol intake within the Zutphen Study during 40 years of follow-up.

Additional analyses showed that the inverse association between wine consumption and mortality was present in all socioeconomic classes. Among manual workers, the HRs for long-term wine consumption were 0.63 (0.31 to 1.30) for CHD, 0.78 (0.49 to 1.23) for CVD and 0.78 (0.54 to 1.12) for all-cause mortality. Among the professionals, the hazard ratios were comparable.

Long-term consumption of alcohol from beer and spirits was not independently related to mortality (table 3.3). However, given the strong correlation between alcohol from spirits and total alcohol intake, these findings should be interpreted with caution. Omiting the adjustment for the prevalence of chronic diseases changed our results slightly but the overall conclusions remained the same.

Alcohol consumption, alcoholic beverages and life expectancy

Men with a long-term alcohol intake less than or equal to 20 grams per day (on average 6 g/d) had a 2.3 years (95%CI: 0.5 to 4.2 years) longer life expectancy at age 50 compared to those who consumed no alcohol. For those men who consumed more than 20 grams of alcohol per day (on average 29 g/d), life expectancy was 1.9 years (-1.1 to 4.9 years) longer compared to non-users.

Men who consumed alcohol from wine, on average 2 g/d, over a longer time period had a 2.5 years longer life expectancy at age 50 (-0.3 to 5.3 years) compared to those who consumed alcohol from beer or spirits (on average about 8 g/d; **figure 3.2**) and a 4.7 years (1.6 to 7.7 years) longer life expectancy compared to no alcohol users.

Table 3.2. Long-term alcohol consumption in relation to cardiovascular and all-cause mortality within the Zutphen Study

		Long-term intake (cumulative average, time-dependent)	
	Amount	**Crude HR (95%CI)**[1]	**Adjusted HR (95%CI)**[2,3]
Coronary heart disease	*>0 to 20 g/d*	0.92 (0.67 to 1.25)	0.80 (0.57 to 1.11)
	>20 g/d	0.80 (0.49 to 1.31)	0.77 (0.44 to 1.33)
Cerebrovascular	*>0 to 20 g/d*	0.44 (0.28 to 0.68)	0.43 (0.26 to 0.70)
	>20 g/d	0.44 (0.22 to 0.92)	0.56 (0.25 to 1.25)
Total cardiovascular	*>0 to 20 g/d*	0.75 (0.60 to 0.95)	0.70 (0.55 to 0.89)
	>20 g/d	0.78 (0.56 to 1.10)	0.83 (0.56 to 1.22)
All Cause	*>0 to 20 g/d*	0.78 (0.65 to 0.93)	0.75 (0.63 to 0.91)
	>20 g/d	0.82 (0.63 to 1.07)	0.82 (0.61 to 1.12)

[1]Crude HR, hazard ratio CI, confidence interval; [2]Hazard ratios are adjusted for former drinking, energy intake without alcohol, the number of cigarettes smoked, cigarette smoking duration, cigar or pipe smoking, intake of vegetables, fruit, fish, saturated fat and *trans* fatty acids, body mass index, prevalence of myocardial infarction, stroke, diabetes mellitus and cancer, and baseline socioeconomic status; [3]Because of missing data in the covariates, the number of events is less than the number mentioned in table 3.1.

Discussion

Long-term light alcohol intake lowered cerebrovascular, total CVD and all-cause mortality risk, and was associated with a longer life expectancy compared to no alcohol intake. Independent of total alcohol intake, wine consumption was strongly and inversely associated with CHD, total CVD and all-cause mortality. For long-term wine consumers, consuming on average less than half a glass of wine per day, life expectancy at age 50 was about 5 years longer compared to no alcohol users.

The major strength of this study was the collection of detailed information on the consumption of different alcoholic beverages at each of seven examination rounds during 40 years of follow-up. This enabled us to study the effects of long-term, i.e. cumulative average, alcohol intake on mortality. The use of cumulative average intakes reduces within-subject variation over time and, thereby, measurement error. The detailed information on potential confounders such as smoking (37-39), diet (40), and socioeconomic status (41) made it possible to study the independent effect of total alcohol intake and alcohol from different types of alcoholic beverages.

The present study also has some weaknesses. First, recent studies have observed that, among men, frequency of alcohol consumption was inversely associated with coronary heart disease risk, independent of the amount of alcohol consumed (42-44). Since in the present study, information on alcohol consumption was collected as part of the usual diet, no data was available on drinking frequency. Second, average long-term alcohol intake in the present study was relatively low and most participants used more than one type of alcoholic beverage in their usual diet. This may have led to less precise estimations of the effect of different types of alcoholic beverages on mortality. Third, for those men who were newly included in the study in 1985, information on alcohol intake was missing in the period 1960-1970. By multiple imputations of total alcohol intake, different types of alcoholic beverages and other dietary covariates in 1960-1970, we were able to counter an underestimation of cumulative

average intake from 1985 onwards for those men who were newly included in the study. We repeated our analysis among the participants who were included in the study from 1960 (*n* = 875) and found similar associations between long-term total alcohol intake and different types of alcoholic beverages, and mortality. Therefore, it is unlikely that the imputation of total alcohol intake, different types of alcoholic beverages and other dietary covariates among those men who were newly included in the study from 1985 biased our results.

Our results confirm the inverse association between moderate alcohol intake, CVD and all-cause mortality risk observed in other studies (38;39;45-53). In contrast to these and other studies (38;39;45;53-56), the highest exposure level was not associated with an increased mortality risk. However, average alcohol intake in the highest exposure level was relatively low (29 g/d) in the Zutphen Study, which may explain the lack of a positive association between

Table 3.3. Long-term consumption of alcohol from beer, wine or spirits in relation to cardiovascular and all-cause mortality within the Zutphen Study

			Long-term intake (cumulative average, time-dependent)		
	Alcohol source	**Amount**	**Crude HR (95% CI)**[1]	**Adjusted HR (95% CI)**[2,3]	**Adjusted HR (95% CI)**[3,4]
Coronary heart disease	*Wine*	*>0 to 20 g/d*	0.59 (0.42 to 0.83)	0.60 (0.41 to 0.87)	0.61 (0.41 to 0.89)
		>20 g/d	NI[5]	NI	NI
	Beer	*>0 to 20 g/d*	0.86 (0.68 to 1.09)	0.79 (0.62 to 1.02)	0.82 (0.60 to 1.12)
		>20 g/d	1.13 (0.41 to 3.08)	1.02 (0.35 to 2.93)	1.10 (0.36 to 3.39)
	Spirits	*>0 to 20 g/d*	0.93 (0.70 to 1.23)	0.85 (0.63 to 1.15)	0.92 (0.63 to 1.34)
		>20 g/d	0.86 (0.40 to 1.84)	0.89 (0.42 to 1.86)	1.01 (0.35 to 2.97)
Cerebro-vascular	*Wine*	*>0 to 20 g/d*	0.67 (0.44 to 1.01)	0.82 (0.53 to 1.26)	0.92 (0.58 to 1.46)
		>20 g/d	NI	NI	NI
	Beer	*>0 to 20 g/d*	0.64 (0.45 to 0.93)	0.62 (0.42 to 0.92)	0.81 (0.48 to 1.35)
		>20 g/d	0.68 (0.09 to 5.01)	0.78 (0.10 to 6.26)	0.78 (0.09 to 6.73)
	Spirits	*>0 to 20 g/d*	0.76 (0.51 to 1.13)	0.79 (0.52 to 1.20)	1.44 (0.72 to 2.86)
		>20 g/d	0.62 (0.19 to 1.97)	0.70 (0.21 to 2.34)	0.93 (0.20 to 4.32)
Total cardio-vascular	*Wine*	*>0 to 20 g/d*	0.63 (0.51 to 0.78)	0.66 (0.52 to 0.84)	0.68 (0.53 to 0.86)
		>20 g/d	1.37 (0.19 to 9.78)	2.45 (0.33 to 18.1)	2.20 (0.30 to 16.4)
	Beer	*>0 to 20 g/d*	0.84 (0.70 to 1.00)	0.82 (0.69 to 0.99)	0.91 (0.72 to 1.14)
		>20 g/d	1.30 (0.62 to 2.74)	1.29 (0.58 to 2.84)	1.26 (0.55 to 2.88)
	Spirits	*>0 to 20 g/d*	0.85 (0.69 to 1.04)	0.82 (0.66 to 1.03)	0.93 (0.70 to 1.24)
		>20 g/d	0.84 (0.50 to 1.41)	0.91 (0.54 to 1.55)	0.88 (0.47 to 1.64)

Table 3.3 continues on the next page.

Continuation of table 3.3

			Long-term intake (cumulative average, time-dependent)		
	Alcohol source	**Amount**	**Crude HR (95% CI)**[1]	**Adjusted HR (95% CI)**[2,3]	**Adjusted HR (95% CI)**[3,4]
All-cause	*Wine*	*>0 to 20 g/d*	0.68 (0.58 to 0.78)	0.72 (0.61 to 0.85)	0.73 (0.62 to 0.87)
		>20 g/d	0.79 (0.11 to 5.59)	1.28 (0.18 to 9.28)	1.21 (0.17 to 8.82)
	Beer	*>0 to 20 g/d*	0.91 (0.80 to 1.05)	0.89 (0.78 to 1.02)	0.98 (0.83 to 1.17)
		>20 g/d	1.41 (0.84 to 2.36)	1.29 (0.76 to 2.19)	1.37 (0.74 to 2.53)
	Spirits	*>0 to 20 g/d*	0.86 (0.75 to 1.00)	0.87 (0.74 to 1.01)	0.97 (0.80 to 1.18)
		>20 g/d	1.08 (0.76 to 1.53)	1.02 (0.67 to 1.55)	1.09 (0.69 to 1.73)

[1]Crude HR, hazard ratio CI, confidence interval; [2]Hazard ratios are adjusted for former drinking, energy intake without alcohol, the number of cigarettes smoked, cigarette smoking duration, cigar or pipe smoking, intake of vegetables, fruit, fish, saturated and *trans* fatty acids, body mass index, prevalence of myocardial infarction, stroke, diabetes mellitus and cancer, and baseline socioeconomic status; [3]Because of missing data, the number of events may be smaller than the number mentioned in table 3.1; [4]Hazard ratios are adjusted for former drinking, energy intake without alcohol, the number of cigarettes smoked, cigarette smoking duration, cigar or pipe smoking, intake of vegetables, fruit, fish, saturated and *trans* fatty acids, body mass index, prevalence of myocardial infarction, stroke, diabetes mellitus and cancer, baseline socioeconomic status, and total alcohol intake; [5]NI, because of the small number of men with >20 g of long-term alcohol intake from wine, the calculated hazard ratios are not informative.

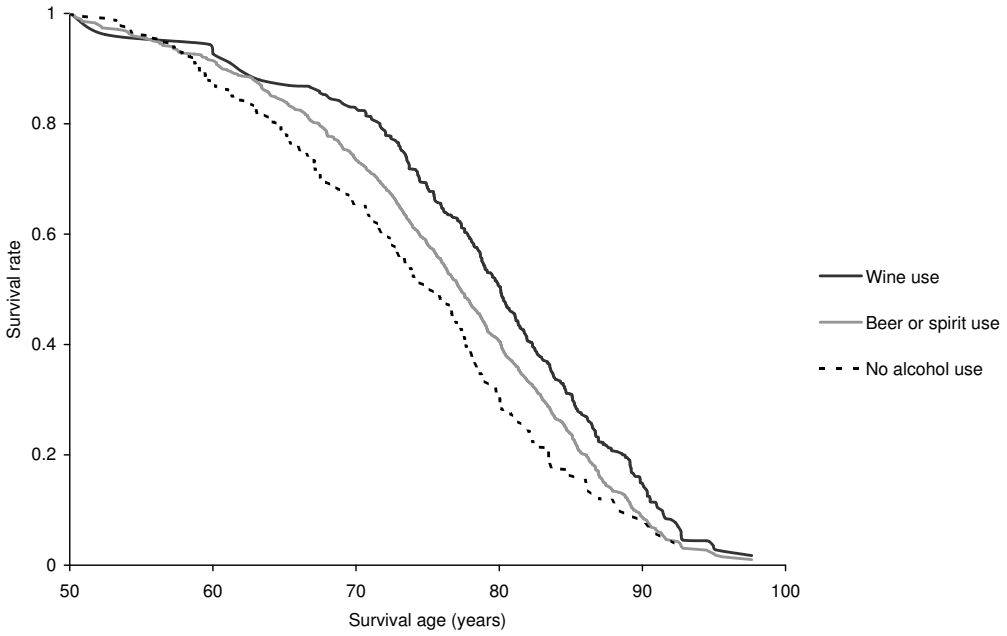

Figure 3.2. Survival curves for men with a long-term consumption of alcohol from wine, beer or spirits, and no alcohol consumers within the Zutphen Study, adjusted for baseline energy intake without energy from alcohol, the number of cigarettes smoked, cigar or pipe smoking, intake of vegetables, fruit, fish, saturated and *trans* fatty acids, body mass index, prevalence of myocardial infarction, stroke, cancer and diabetes mellitus, and socioeconomic status.

mortality and a higher intake level. In their meta-analysis, Corrao *et al.* estimated that the risk of CHD mortality is lowest at 16 grams per day with a corresponding hazard ratio of 0.84 (57). In the present study, the hazard ratios for CHD mortality were comparable but not statistically significant (table 3.2).

Smoking might confound the association between alcohol intake and mortality. Previous results from the Zutphen Study indicated that the number of cigarettes smoked as well as the duration of cigarette smoking are, independently of each other, associated with mortality (58). In our multivariable analyses, we adjusted for these aspects of smoking. So, it is not likely that the association between alcohol intake and mortality is explained by confounding due to smoking.

In the present study, wine consumption was associated with a lower mortality risk, independent of total alcohol intake. Some studies did not demonstrate a favourable effect of one specific type of alcoholic beverage over another (14;42), while others found an inverse and independent association between wine consumption and mortality (13;59-61). In the present study, 70% of all wine consumed was red wine. This suggests that the cardioprotective effect of wine could be due to a protective effect of polyphenolic compounds in red wine, but other explanations can not be ruled out.

Socioeconomic status might confound the association between wine consumption and mortality. However, in our multivariable analyses we adjusted for socioeconomic status, based on occupation at baseline. At the start of the present study, the men were already in a later phase in their careers and baseline socioeconomic status was considered to be a good indicator during the follow-up period. Furthermore, the increase in the percentage of wine users during follow-up was observed in all levels of socioeconomic status, and additional stratified analyses showed that the inverse association between wine consumption and mortality was present in all socioeconomic classes. These results suggest that the association between wine consumption and mortality can not be explained by confounding due to socioeconomic status.

Long-term wine consumers had about 5 years longer life expectancy at age 50 compared to no alcohol users. Of these 5 years, about 2 years can be attributed to an effect of alcohol intake and is in accordance with the inverse association between long-term alcohol intake and all-cause mortality found in the present study. The remainder 3 years can be attributed to an effect of wine consumption. However, given the wide confidence interval, the effect of wine as such may be overestimated. To our knowledge, we are the first who studied the effects of absolute alcohol intake and type of alcoholic beverage on life expectancy and more studies are needed to verify our results.

In conclusion, long-term light alcohol intake is associated with a lower risk of cardiovascular and all-cause mortality risk, and a longer life expectancy. The inverse associations between wine consumption and mortality remained after adjustment for total alcohol intake. Wine consumers had a 5 years longer life expectancy compared to no-alcohol consumers; however, more studies are needed to draw conclusions on the strength of the association between wine consumption and mortality.

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Chapter 4

Long-term *trans* unsaturated fatty acid intake and 40-y (sudden) coronary heart disease death: The Zutphen Study

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Abstract

Aim: We aimed to describe the change in long-term *trans* unsaturated fatty acid intake and to assess the relation between recent and long-term *trans* unsaturated fatty acid intake and (sudden) coronary heart disease death.

Methods and Results: Changes in *trans* unsaturated fatty acid intake and the effects of recent and long-term *trans* unsaturated fatty acid intake on (sudden) coronary heart disease death were investigated in the Zutphen Study, a cohort of 1373 men born between 1900 and 1920, and examined repeatedly between 1960 and 2000. Hazard ratios were obtained from time-dependent Cox regression models. Average energy intake from *trans* unsaturated fatty acids decreased from 7% in 1960 to about 1% in 2000. Each 2% increase in long-term energy intake from *trans* unsaturated fatty acids was positively associated with sudden coronary death (hazard ratio: 1.62 [95% CI: 1.01 to 2.60]). We observed no associations between *trans* unsaturated fatty acid intake and sudden death from other causes, nonsudden coronary death and total coronary death.

Conclusions: Average *trans* unsaturated fatty acid intake decreased remarkably in the Zutphen Study between 1960 and 2000. Long-term *trans* unsaturated fatty acid intake is positively associated with sudden coronary death but not with nonsudden and total coronary death.

Introduction

Results from several studies suggest that *trans* unsaturated fatty acids are strongly associated with the risk of coronary heart disease (CHD). This possibility is consistent with findings from clinical trials showing that these fatty acids increase LDL cholesterol and lower HDL cholesterol concentrations in blood (1) and negatively affect other risk factors such as inflammation and endothelial function (2). In prospective studies, each 2% increase in energy intake from *trans* unsaturated fatty acids was associated with a 23% increase in the incidence of CHD (3). Little is known about the effects of *trans* unsaturated fatty acid intake on sudden coronary death.

For cohort studies in which *trans* unsaturated fatty acid intake is assessed only at the baseline examination, consumption patterns and product composition are assumed to be relatively constant over the entire study period. However, it is unlikely that one exposure measurement in the past accurately reflect long-term *trans* unsaturated fatty acid intake, because consumption patterns change during the course of a life. Furthermore, it is known that the *trans* unsaturated fatty acid content of foods has changed (4;5). To obtain correct estimates of the long-term effects of *trans* unsaturated fatty acid intake, repeated measures and time-specific food-composition tables are needed (6;7). Moreover, the use of repeated measures, especially the cumulative average method, reduces within-subject variation over time and, thereby, reduces misclassification of *trans* unsaturated fatty acid intake (8).

The objective of the present study was to assess the relation between recent and long-term *trans* unsaturated fatty acid intake and (sudden) coronary heart disease death. For this purpose, we used 7 repeated measures of *trans* unsaturated fatty acid intake.

Methods

Study population

The Zutphen Study started as the Dutch contribution to the Seven Countries Study, a longitudinal study of the relations among diet, other risk factors and chronic diseases (9). The Zutphen Study has been carried out since 1960 among middle-aged men in Zutphen, an old industrial town in the eastern part of the Netherlands with ≈30 000 inhabitants. In 1960, a random sample was drawn of 1088 men born between 1900 and 1919 and residing for ≥5 y in Zutphen. Of those men, 878 participated in the Zutphen Study (response rate: 81%), and 872 took part in both dietary and physical examinations. The examinations were repeated in 1965 and 1970. In 1985, the group of 554 survivors was extended with a new random sample of men of the same birth cohort. Of the 1266 men who were invited, 939 participated (response rate: 74%), and 825 took part in both dietary and physical examinations. These examinations were repeated in 1990, 1995 and 2000.

Baseline data were collected in 1960, before the Helsinki Declaration was developed, and oral consent was obtained for follow-up data. In 1985 and 1990, the study was approved by the Medical Ethics Committee of the University of Leiden (Leiden, Netherlands), and, in 1995 and 2000, by the Medical Ethics Committee of the Netherlands Organisation for Applied Scientific Research.

Assessment of food consumption and *trans* unsaturated fatty acid intake

In all dietary surveys, information on habitual food consumption was collected by using the cross-check dietary history method (10), adapted to the Dutch diet (11). This method provides information about the participant's usual food consumption pattern, 6-12 mo before the interview. From 1985 onwards, the information about the usual food consumption pattern was limited to the month before the interview because consumption patterns were much more complicated than those in the 1960s. The interviews were carried out by experienced dieticians in the spring and early summer. Each participant was interviewed, if possible in the presence of his wife, about his usual food consumption during weekdays and on weekends. On the basis of this daily pattern, average food consumption during a day or week (the first check) and the quantity of foods bought per week (the second check) were estimated and presented to the participants for calculation and verification of their food consumption.

The daily intakes of *trans* unsaturated fatty acids, total energy, and other nutrients were calculated by using time-specific food composition tables to account for changes in product composition and qualitative improvements in analytic methods (12-18). Because the *trans* unsaturated fatty acid content of foods was not analyzed before the 1980s, we used a time-specific food composition table from 1985 to calculate total *trans* unsaturated fatty acid intake in 1960, 1965, and 1970 (16).

Assessment of potential confounders

Detailed information on type and amount of smoking was collected by using standardized questionnaires (19). Information on alcohol intake was obtained from the cross-check dietary history method (20). During physical examinations, men's weight and height were measured and body mass index (BMI; in kg/m^2) was calculated. Information on the prevalence of myocardial infarction, stroke, diabetes mellitus, and cancer was collected throughout the study. The men were classified into 4 levels of socioeconomic status according to their occupation at baseline.

Case ascertainment

Participants were followed until death, or censored on June 30, 2000. Three participants were lost to follow-up during the study and were censored after their last physical examination. The final causes of death were ascertained by one clinical epidemiologist (AM) and coded according to the Eighth Revision of the International Classification of Diseases (21). Because the underlying cause of death in elderly people is often difficult to ascertain, we included both primary and secondary causes of death in our analyses. CHD deaths, including cases of sudden death, were coded 410–414. Men who died within 2 h after onset of symptoms that were highly likely to be coronary and those with a past diagnosis of CHD were called sudden coronary deaths. Other cases of sudden death were classified as sudden death from other causes.

Statistical analysis

First, Cox proportional hazard analyses were performed with age as the time variable, and with updated information on *trans* unsaturated fatty acid intake at each round of measurement (most recent intake). Second, the cumulative average *trans* unsaturated fatty acid intake was used to better represent long-term intake (8). For those men who were newly included

in the study in 1985, information on food consumption and *trans* unsaturated fatty acid intake was missing for 1960-1970. Because average *trans* unsaturated fatty acid intake was lower in 1985 than in 1960-1970, the use of cumulative averages excluding earlier intakes in those men who were newly included in the study in 1985 would underestimate their intakes as compared with those of men included in 1960. To adjust for this underestimation, the process of multiple imputation (22) of *trans* unsaturated fatty acid intake and dietary covariates between 1960 and 1970 was carried out 5 times in those men who were newly included in 1985, by using an adapted version of predicted mean matching (LG Lazzeroni *et al*., unpublished observations, 1990). The SAS code (SAS Institute, Cary, NC) that was used for the multiple imputation can be downloaded (Internet: www.rivm.nl/sasmacros).

For Cox proportional hazard models, the PHREG procedure of SAS/STAT software (Version 9.1; SAS Institute, Inc, Cary, NC) was used. The nutrient density method was used to adjust *trans* unsaturated fatty acid intake for total energy intake; participants were grouped into 4 categories of intake: ≤4%, 4-6%, 6-8%, and >8 % of energy. HRs were calculated by using the lowest intake category as the reference group and were calculated continuously for every 2% increase in energy intake from *trans* unsaturated fatty acids. The covariates in the model were total energy intake without energy from alcohol (kcal), alcohol intake (indicator variables for 0, >0-20, or >20 g), wine use (yes or no), consumption of fruit and vegetables (g), BMI (in kg/m2), cigar or pipe smoking (never or long-term former, recent former, or current) (19), cigarette smoking duration (divided by 10 y), the daily number of cigarettes smoked (divided by 10), the use of a serum cholesterol lowering diet (yes or no), the prevalence of diabetes mellitus (yes or no) and baseline socioeconomic status (indicator variables for manual workers, non-manual workers, small-business owners and professionals). To estimate the effects of substituting *trans* unsaturated fatty acids for *cis* unsaturated fat to keep saturated fat intake constant, the models were also adjusted for the sum of *trans* unsaturated fatty acid, *cis* monounsaturated and *cis* polyunsaturated fat intake and for total saturated fat intake (% of energy). The effects of substituting *trans* unsaturated fatty acids for saturated fat, and thus of keeping *cis* unsaturated fat constant, were estimated in a similar way.

In the analyses of the most recent intakes, all covariates were updated in each round of measurement, and all available data were used for the analyses. In the analyses of long-term intake, the cumulative average intake of all dietary covariates was calculated up to each measurement round, and non-dietary covariates were updated in each round of measurement. Because multiple imputations yielded 5 versions of the dataset, analyses of long-term *trans* fatty acid intake were performed 5 times and the results were pooled by using the MIANALYZE procedure of SAS/STAT software (Version 9.1; SAS Institute, Inc, Cary, NC).

Results

Population characteristics

During 40 y of follow-up (average survival age: 77 y), 1130 of the 1373 men participating in the Zutphen Study died (**table 4.1**). A total of 348 men died of CHD, of these deaths 66 were sudden coronary deaths (19% of all CHD deaths) and 46 were sudden deaths due to other causes (13%).

Table 4.1. Characteristics of participants in the Zutphen Study by year of measurement[1]

	Cohort	**1960**	**1965**	**1970**	**1985**	**1990**	**1995**	**2000**	P_{trend}[2]
Participants (*n*)	*1960*	872	721	615	349	231	114	51	
	1985				476	306	161	68	
Cumulative deaths (*n*)									
All-cause		-	40	103	412	645	889	1130	
All coronary heart disease		-	13	40	176	231	297	348	
Sudden coronary[3]		-	7	19	62	62	64	66	
Sudden from other causes[4]		-	1	2	22	39	44	46	
Age (y)[5]		49 ± 6[6]	54 ± 5	59 ± 5	71 ± 5	75 ± 5	80 ± 4	83 ± 3	<.0001
Energy intake without alcohol (kcal)		3082 ± 673	2920 ± 674	2539 ± 539	2146 ± 506	2029 ± 458	2029 ± 468	1991 ± 457	<.0001
***trans* Unsaturated fatty acids**	*1960*	19 ± 6	18 ± 7	14 ± 6	11 ± 6	8 ± 4	5 ± 2	4 ± 1	<.0001
(g/2500 kcal of total energy intake)	*1985*	-	-	-	12 ± 6	8 ± 4	5 ± 2	3 ± 1	
Alcohol intake (gram)		4 ± 10	6 ± 11	9 ± 12	13 ± 17	10 ± 14	11 ± 14	12 ± 14	<.0001
Wine users (%)		2	5	6	23	29	34	44	<.0001
BMI (kg/m2)		24.1 ± 2.7	24.9 ± 2.7	25.2 ± 2.8	25.5 ± 3.1	25.5 ± 3.2	25.3 ± 3.4	26.0 ± 3.3	<.0001
Overall smoking (%)[7]									
Never and long-term former		6	6	9	26	50	60	72	<.0001
Recent former		6	11	15	31	17	16	14	<.0001
Cigarettes		74	61	53	30	23	18	6	<.0001
Cigars or pipes		14	21	23	13	10	6	8	0.0002

[1]All participants were men; [2]Assessed by using generalized estimating equations; [3]Defined as cases of sudden death with a high likelihood to be coronary, occurring within 2h of the onset of symptoms in diagnosed cases or in persons with a past diagnosis of coronary heart disease; [4]Defined as cases of sudden death after reasonable exclusion of cardiac-specific etiologies; [5]Defined as age on December 31st of the year before the year of examination; [6]Mean ± SD (all such variables); [7]Never and long-term former smokers are defined as men who never smoked or stopped smoking ≥10 ys ago. Recent former smokers are defined as men who stopped smoking <10 y ago.

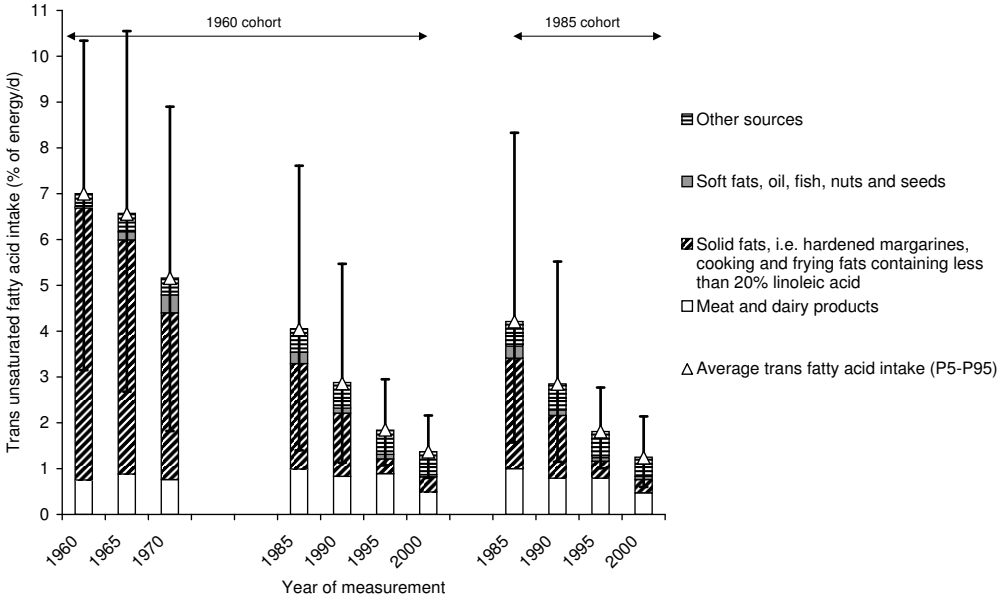

Figure 4.1. Changes in *trans* unsaturated fatty acid intake in subjects in the Zutphen Study (*n* = 1373), during 40 y of follow-up.

In the participants who were included in the study in 1960 and who survived to 2000, average *trans* unsaturated fatty acid intake decreased remarkably from 19 g/2500 kcal of total energy intake in 1960 (≈7% of energy) to 4 g/2500 kcal of total energy intake (≈1% of energy) in 2000 (table 4.1). Among those men who were newly included in the study in 1985, the intake of *trans* unsaturated fatty acids was comparable. Until 1990, solid fats –e.g. hardened margarines and cooking and frying fats containing less than 20% linoleic acid– were the major source of *trans* unsaturated fatty acid intake (48-85% of the total intake), after which meat and dairy products became the major source (36-48% of the total intake; **figure 4.1**). The correlation coefficients between *trans* unsaturated fatty acid intake decreased from approximately 0.4 for measurements 5 y apart, 0.3 for measurements 10 y apart to <0.3 for measurements >15 y apart.

Trans unsaturated fatty acid intake and (sudden) coronary heart disease death

Long-term energy intake from *trans* unsaturated fatty acids was significantly related to sudden coronary death (**table 4.2, figure 4.2**). After adjustment for potential confounders, each 2% increase in long-term energy intake from *trans* unsaturated fatty acids was positively associated with sudden coronary death (HR: 1.62 [95% CI: 1.01 to 2.60). This association was independent of age. Since all sudden coronary deaths occurred among the participants who were included in the study from 1960, we repeated our analyses among these men (*n* = 875) and found a similar association. (HR: 1.49 [0.96 to 2.31]). Moreover, a similar association was found when *trans* unsaturated fatty acids were substituted for saturated fat, keeping the intake of *cis* unsaturated fat constant (HR: 1.61 [0.95 to 2.74]). Long-term *trans* unsaturated fatty acid intake was not associated with sudden death from other causes (figure 4.2), nonsudden CHD death (figure 4.2) and total CHD death (table 4.2, figure 4.2).

Table 4.2. Long-term *trans* unsaturated fatty acid intake in relation to 40-y sudden coronary and total coronary heart disease ([CHD] sudden and nonsudden combined) deaths within the Zutphen Study[1]

Cause of death	Unit	HR [2]	95% CI	HR [3,4]	95% CI	HR [3,5]	95% CI
Sudden coronary (n = 66)							
	≤4% of energy	1.00	—	1.00	—	1.00	—
	4-6% of energy	2.05	0.61 to 6.93	2.26	0.54 to 9.57	2.54	0.56 to 11.6
	6-8% of energy	2.40	0.71 to 8.09	2.07	0.48 to 8.85	2.51	0.50 to 12.7
	>8% of energy	5.12	1.50 to 17.5	4.12	0.94 to 18.0	5.58	0.92 to 33.7
	Per 2% of energy	1.59	1.22 to 2.08	1.38	1.02 to 1.88	1.62	1.01 to 2.60
	P for trend[6]		0.001		0.04		0.04
CHD (n = 348)							
	≤4% of energy	1.00	—	1.00	—	1.00	—
	4-6% of energy	1.16	0.79 to 1.71	1.07	0.68 to 1.68	1.02	0.65 to 1.60
	6-8% of energy	1.25	0.83 to 1.88	1.06	0.66 to 1.72	0.97	0.59 to 1.58
	>8% of energy	1.49	0.94 to 2.36	1.21	0.70 to 2.07	1.04	0.57 to 1.90
	Per 2% of energy	1.15	1.00 to 1.32	1.06	0.90 to 1.25	1.01	0.82 to 1.24
	P for trend[6]		0.05		0.47		0.91

[1]n = 1373. HR to hazard ratio to obtained from time-dependent Cox proportional hazard model. For long-term intake to the cumulative average intake of all dietary covariates was calculated and non-dietary covariates were updated at each measurement round; [2]Crude HRs; [3]Because of missing data in the covariates, the number of events was less in the adjusted analyses: i.e. 336 CHD deaths and 63 sudden coronary deaths; [4]Adjusted for total energy intake without alcohol; alcohol intake; wine use; fruit and vegetable intakes; use of a serum cholesterol-lowering diet; cigarette smoking duration and the number of cigarettes smoked/d; cigar or pipe smoking; BMI; prevalence of diabetes mellitus; and socioeconomic status; [5]Also adjusted for total saturated fat intake and the sum of *trans* unsaturated fatty acid; *cis* monounsaturated fat; and *cis* polyunsaturated fat intake; [6]Assessed by modelling *trans* unsaturated fatty acid intake continuously.

We observed no associations between recent energy intake from trans unsaturated fatty acids and (sudden) coronary death (data not shown).

Discussion

We observed a decrease in the average energy intake from *trans* unsaturated fatty acids from 7% to about 1% between 1960 and 2000 in the participants in the Zutphen Study, the Netherlands. Each 2% increase in long-term energy intake from *trans* unsaturated fatty acids was associated with a 62% increase in the risk of sudden coronary death. Long-term *trans* unsaturated fatty acid intake was not associated with sudden death from other causes, nonsudden CHD death and with total CHD death.

The major strength of this study was the collection of detailed information on usual dietary intake at each of 7 rounds of examination and on coronary death during the 40 y of follow-up. This enabled us to study recent and long-term –i.e. cumulative average– *trans* unsaturated fatty acid intake in relation to (sudden) coronary death. The detailed information on potential confounders made it possible to study the independent relations of trans unsaturated fatty acids with mortality.

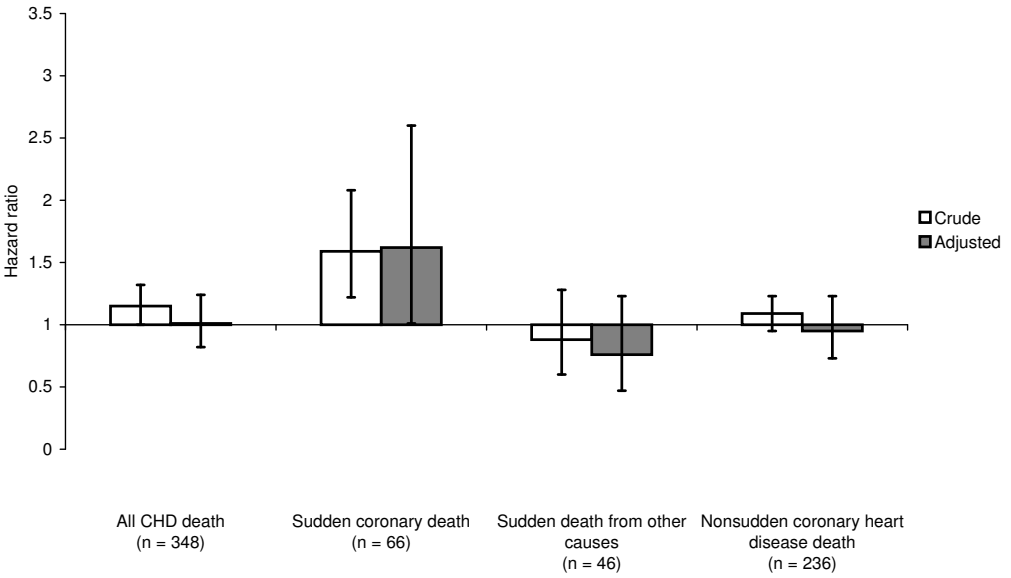

Figure 4.2. Hazard ratios with 95% CIs, obtained from time-dependent Cox proportional hazard models, for every 2% increase in long-term energy intake from *trans* unsaturated fatty acids in relation to 40-y sudden and nonsudden coronary heart disease (CHD) deaths within the Zutphen Study (*n* = 1373). Hazard ratios were adjusted for the sum of *trans* unsaturated fatty acid and *cis* unsaturated fat intake; total saturated fat intake; total energy intake without alcohol; alcohol intake; wine use; fruit and vegetable intakes; the use of a serum cholesterol-lowering diet; cigarette smoking duration and the number of cigarettes smoked/d; cigar or pipe smoking; BMI; prevalence of diabetes mellitus; and socioeconomic status. Because of missing data in covariates, the number of events was less in the adjusted analyses: i.e. 336 CHD deaths, 63 sudden coronary deaths, 45 sudden deaths from other causes and 228 nonsudden CHD deaths. Sudden coronary deaths were defined as cases of sudden death that were highly likely to be coronary and that occurred within 2 h of the onset of symptoms in diagnosed cases or in persons with a past diagnosis of CHD. Sudden deaths from other causes were defined as cases of sudden death only after a reasonable exclusion of cardiac specific causes.

The present study also had some weaknesses. First, *trans* unsaturated fatty acid intake was calculated by using time-specific food composition tables, but the *trans* unsaturated fatty acid content of foods was not available before 1980s. For the period of 1985 to 1995, Oomen *et al.* created 3 time-specific tables (16). We used the table for 1985 to calculate total *trans* unsaturated fatty acid intake in 1960–1970. Because solid edible fats –i.e. hardened margarines, cooking and frying fats containing less than 20% linoleic acid– were the major source of total *trans* unsaturated fatty acid intake from 1960 to 1970 and in 1985 (figure 4.1), we considered the estimation of total *trans* unsaturated fatty acid intake for 1960–1970 valid. Second, for those men who were newly included in the study in 1985, information on *trans* unsaturated fatty acid intake was missing for 1960–1970. By using a process of multiple imputation of *trans* unsaturated fatty acid intake and other dietary covariates in 1960-1970, we were able to counter an underestimation of cumulative average intake from 1985 onwards for those men who were newly included in the study. However, the assumptions that were made in the multiple imputation method may have led to less precise effect estimates. Without imputation of the *trans* unsaturated fatty acid intake and other dietary covariates, the associations changed slightly, but the overall conclusions remained the same. Therefore, it is unlikely that bias occurred. Third, information on physical activity was not collected continuously during the whole follow-

up period and, therefore, repeatedly collected data was not available for the present study.

In the present study, we observed a remarkable decrease in average intake of *trans* unsaturated fatty acids between 1960 and 2000 from 7 to about 1%. In the 1960s, the intake of *trans* unsaturated fatty acids in Zutphen was the highest in the 16 cohort of the Seven Countries Study (23). The chemical analyses of a food composite representing the average food consumption pattern of the Zutphen men in 1960 obtained an intake of 8% of energy and is similar to the 7% obtained by calculation from the food composition tables in the present study. This very high intake of *trans* unsaturated fatty acid intake in the Netherlands in the 1960s was due to the high content of hydrogenated fish oils in solid fats. The present study showed that there was a considerable decrease in *trans* unsaturated fatty acid intake in the Netherlands between 1960 and 2000, and started already before the decision of the Dutch margarine producers in 1994 to reduce the *trans* unsaturated fatty acid content in margarines (24;25).

We found that each 2% increase in long-term energy intake from *trans* unsaturated fatty acids increased sudden coronary death risk by 62%. Similar results were obtained in case-control studies of biomarkers of *trans* unsaturated fatty acid intake. In these studies, the strongest associations were found for levels of C18:2 *trans* unsaturated fatty acids (26;27). For total *trans* unsaturated fatty acid intake, the associations were modest (27). To our knowledge, we are the first to examine the associations between dietary *trans* unsaturated fatty acid intake and sudden coronary death in detail in a prospective cohort study. Other studies are needed to verify our results.

The primary cause of sudden coronary death is ventricular fibrillation and studies have shown that free fatty acids have arrhythmogenic properties, due to the interaction with biological membranes, i.e. lipid bilayers with two hydrophilic surfaces and a hydrophobic core. Especially the hydrophobic portions of membrane proteins interact with lipids in the core of the bilayer (28). These membrane proteins include the voltage-gated ion channels responsible for the cardiac action potential. Alterations in membrane composition, which occur when free fatty acids are incorporated in the bilayer, change closing and inactivation of the ion channels (28). The arrhythmogenic properties of fatty acids depend on their fatty acyl chain length and degree of de-saturation (29;30). Fatty acids with a shorter chain length and a lower degree of de-saturation may enhance calcium transport in the biological membranes (30). Furthermore, unsaturated fatty acids with a *trans* configuration may also promote calcium transport compared to unsaturated fatty acids with a *cis* configuration, independent of fatty acyl chain length (31). Therefore, it is hypothesized that *trans* unsaturated fatty acids may have proarrhytmic properties and may increase the risk of sudden coronary death (32).

Our results did not confirm those of an earlier analysis of the Zutphen Elderly Study in which a positive relation was found between *trans* unsaturated fatty acid intake, and fatal and nonfatal CHD in the period 1985-1995 (33). In the present study, average *trans* unsaturated fatty acid intake decreased from 7% to ≈1% of energy between 1960 and 2000, and was primarily the result of changes in the composition of solid fats (4;5). This remarkable decrease resulted in low correlation coefficients for *trans* unsaturated fatty acid intake between measurements rounds, when time between rounds became longer (approximately 0.4 for measurements 5 y apart, 0.3 for measurements 10 y apart to <0.3 for measurements >15 y apart). This could be

the reason for the absence of a relation between long-term *trans* unsaturated fatty acid intake and CHD death in the present study.

We conclude that in the Netherlands, a remarkable decrease in average energy intake from *trans* unsaturated fatty acids was observed from 7 to about 1%. We also found that long-term *trans* unsaturated fatty acid intake was positively associated with the risk of sudden coronary death. We did not find an association between long-term *trans* unsaturated fatty acid intake and total CHD death.

Conflict of interest: None declared.

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Chapter 5

Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen Study

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Eur Heart J 2008;29:2024-30

Abstract

Aims: To assess the relationship between fish consumption or eicosapenaenoic acid (EPA)+docosahexaenoic acid (DHA) intake from fish, and (sudden) coronary death.

Methods and results: The impact of recent and long-term fish consumption and EPA+DHA intake on (sudden) coronary death was investigated in the Zutphen Study, a cohort of 1373 men born between 1900 and 1920, and examined repeatedly between 1960 and 2000. Hazard ratios were obtained from time-dependent Cox regression models. The associations between long-term fish consumption, EPA+DHA intake, and (sudden) coronary death were stronger than those of recent consumption. Long-term fish consumption was inversely associated (borderline significant) with coronary heart disease (CHD) death; however, the strength of the association decreased from age 50 (HR: 0.32 [95%CI: 0.13 to 0.80]) until age 80 (HR: 1.34 [0.58 to 3.12]). For men with a daily EPA+DHA intake from fish below 250 mg compared with no intake, CHD death risk was reduced to the same extent as for men with a daily intake above 250 mg (*P*-value for trend: 0.27). Moreover, long-term fatty-fish consumption lowered the risk of sudden coronary death (HR: 0.46 [0.27 to 0.78]).

Conclusion: The strength of the association between long-term fish consumption and CHD death decreased with increasing age. Fatty-fish consumption lowered sudden coronary death risk. There was no clear dose-response relationship between EPA+DHA intake and (sudden) coronary death.

Introduction

In most prospective cohort studies, consuming a relatively small amount of fish or fish oil was associated with a lower risk of coronary heart disease (CHD) death (1) and these results were confirmed by several intervention studies (1-5). In a meta-analysis of cohort studies, He *et al*. (1) estimated that consuming fish once a week lowers CHD death risk by 15%. In addition, Mozaffarian and Rimm (5) estimated, by combining results from both randomized trials and prospective cohort studies, that consuming 250 mg eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA) per day lowers CHD death risk by 36%.

EPA (C20:5n-3) and DHA (C22:6n-3), two long-chain n-3 polyunsaturated fatty acids mainly found in fatty fish, are the constituents in fish oil that may reduce the risk of CHD death. The most likely explanation by which relatively small amounts of EPA and DHA reduce the risk of CHD death are their anti-arrhythmic properties (6). They are also suggestive for an inverse relation with sudden coronary death (7;8). In observational studies, consuming fish once or twice a week was associated with a 42-50% lower risk of sudden coronary death or cardiac arrest (9-11). The associations with blood (12) or cell membrane (10) levels of EPA+DHA were even stronger. However, little is known about the effect of long-term fish consumption or EPA+DHA intake on (sudden) coronary deaths.

For prospective studies in which fish consumption is only assessed at the baseline examination, consumption patterns are assumed to be relatively constant over the entire study period. However, it is unlikely that exposure measurements in the past accurately reflect long-term fish consumption since consumption patterns change during life. To get correct estimates of the long-term effects of fish consumption and EPA+DHA intake, repeated measures are needed (13;14).

The objective of the present study is to assess the relationship between recent and long-term fish consumption or EPA+DHA intake from fish, and (sudden) coronary death. For this purpose, we used up to seven repeated measures of fish consumption and EPA+DHA intake from fish collected during 40 years of follow-up in a cohort of middle-aged men.

Methods

Study population

The Zutphen Study started as the Dutch contribution to the Seven Countries Study, a longitudinal study of the relationships between diet, other risk factors and chronic diseases (15). The Zutphen Study has been carried out since 1960 among middle-aged men in Zutphen, an old industrial town in the eastern part of the Netherlands with about 30 000 inhabitants. In 1960, a random sample was drawn of 1088 men born between 1900 and 1919 and residing for at least 5 years in Zutphen. Of those men, 878 participated in the Zutphen Study (response rate: 81%) and 872 took part in both dietary and physical examinations. These examinations were repeated in 1965 and 1970. In 1985, the group of 554 survivors was extended with a new random sample of men of the same birth cohort. Of the 1266 men who were invited, 939 men participated (response rate: 74%) and 825 men took part in both dietary and physical examinations. These examinations were repeated in 1990, 1995 and 2000.

Baseline data was collected in 1960 before the Helsinki Declaration was developed and oral consent was obtained in view of follow-up data. In 1985 and 1990, the study was approved

by the Medical Ethics Committee of the University of Leiden, The Netherlands, and in 1995 and 2000, by the Medical Ethics Committee of the Netherlands Organisation for Applied Scientific Research (TNO).

Assessment of fish consumption and fish fatty acid intake

Information on the habitual food consumption was collected by using the cross-check dietary history method (16), adapted to the Dutch situation (17;18). This method provides information about the participant's usual food consumption pattern, 6-12 months preceding the interview. From 1985 onwards, the information about the usual food consumption pattern was limited to the month preceding the interview because consumption patterns from 1985 were much more complicated than those in the 1960s. The interviews were carried out by experienced dieticians in spring and early summer. Each participant, if possible in the presence of his wife, was interviewed about his usual food consumption during weekdays and weekends. Based on this daily pattern, average food consumption during a day or week (first check) and the quantity of foods bought per week (second check) was estimated and presented to the participants to calculate and verify the participants' food consumption. Total fish consumption was divided into fatty (e.g. salmon, mackerel, herring, eel, and sardines) and lean (e.g. codfish, plaice and pollack) fish. The daily intake of EPA+DHA from fish in the period 1960-1995 was calculated using the digital update of the Dutch food composition table from 1996 (19;20). The daily intake of EPA+DHA from fish in 2000 was calculated using the Dutch food composition table from 2001 (21).

Assessment of potential confounders

In all dietary surveys, habitual food consumption and the use of a prescribed diet was recorded (17;18). The daily intake of energy and nutrients (including alcohol) was calculated using food composition tables close to the year of measurement. Detailed information on the type and amount of smoking was collected using standardized questionnaires (22). During physical examinations, men's blood pressure, weight, and height were measured and body mass index (BMI) was calculated (kg/m^2). Information on the prevalence of diabetes mellitus and other chronic diseases was collected and verified by contacting each participant's general practitioner (23). The men were classified into four levels of socioeconomic status according to occupation at baseline (24).

Case ascertainment

Participants were followed until death, or censored on 30 June, 2000. Three participants were lost to follow-up during the study and were censored after their last physical examination. The final causes of death were ascertained by one clinical epidemiologist and coded according to the Eight Revision of the International Classification of Diseases (25). Because the underlying cause of death in elderly people is often difficult to establish, we included both primary and secondary causes of death in our analyses. CHD deaths were coded 410-414, including cases of sudden death. Men who died within 2 h after onset of symptoms with a high likelihood to be coronary and those with a past diagnosis of CHD were called sudden coronary deaths.

Statistical analysis

Cox proportional hazard analyses with age until death or censor date as the time variable (26;27) were performed using the PHREG procedure of SAS/STAT software (version 9.1; SAS Institute, Inc., Cary, NC). First, we used most recent information on fish consumption and EPA+DHA intake from fish (time-dependent variables). Second, we calculated cumulative average fish consumption and EPA+DHA intake from fish to better represent long-term intake (28). With this method, (sudden) coronary death between 1960 and 1965 was related to fish consumption from the 1960 examination round; (sudden) coronary death between 1965 and 1970 was related to average fish consumption from the 1960 and 1965 examination rounds; mortality between 1970 and 1985 was related to average fish consumption from the 1960, 1965 and 1970 examination rounds, and so on. For those men who were newly included in the study in 1985, information on fish consumption and EPA+DHA intake from fish was missing in the period 1960-1970. Since average EPA+DHA intake from fish was lower in 1985 than in 1960-1970, taking cumulative averages excluding earlier intakes in those men who were newly included in the study in 1985 would underestimate their intakes compared with men included in 1960. To account for this underestimation, multiple imputation (5 times) (29) of fish consumption, EPA+DHA intake from fish, and other dietary covariates between 1960 and 1970 was carried out among those men who were newly included in 1985, with an adapted version of predicted mean matching (30). For each missing observation, the nearest –in terms of predicted value– non-missing observation was drawn and assigned as the imputed value to the missing observation. The variables, besides fish consumption, EPA+DHA intake, and all dietary covariates, that were used to impute the missing observations were age at start and end of follow-up, and the indicator variable for (sudden) coronary death. The SAS code that was used for the multiple imputation can be downloaded from www.rivn.nl/sasmacros. Analyses on long-term, i.e. cumulative average, fish consumption and EPA+DHA intake from fish were performed on five imputed datasets and results were pooled using the MIANALYZE procedure of SAS/STAT software. For both recent and long-term fish consumption and EPA+DHA intake, time of follow-up started at the moment the men were included in the study.

The participants were divided into consumers and non-consumers of, respectively, total fish, fatty fish and lean fish according to their recent and long-term, i.e. cumulative average, fish consumption. Additionally, participants were grouped into three groups according to their recent and long-term intake of EPA+DHA from fish: 0, >0-250, and >250 mg (5). Hazard ratios were calculated using the non-consumers and the no intake category as the reference categories. For EPA+DHA intake from fish, a *P*-value for trend was calculated using the continuously distributed variable. A two-sided *P*-value <0.05 was considered statistically significant.

The covariates in the multivariable models were total energy intake (kcal per day), alcohol intake (indicator variables for 0, >0-20, >20 g per day), wine use (yes or no), fruit and vegetable consumption (gram per day), saturated fat, *trans* unsaturated fatty acid, *cis* monounsaturated fat and *cis* polyunsaturated fat intake (gram per day), use of a serum cholesterol lowering diet (yes or no), cigar or pipe smoking (never or long-term ex, recent-ex or current) (22), cigarette smoking duration (divided by 10), the daily number of cigarettes smoked (divided by 10), BMI (kg/m^2), prevalence of diabetes mellitus (yes or no), systolic blood pressure (mmHg), and baseline socioeconomic status (indicator variables for manual workers, non-manual workers, small-business owners, and professionals). The separate models for fatty and lean

fish consumption were additionally adjusted for each other. In the analyses for the most recent intake, all covariates were updated at each measurement round. In the analyses for long-term intake, the cumulative average intake of all dietary covariates was calculated and non-dietary covariates were updated at each measurement round. To test whether the associations were constant over our time variable (age), a product term between fish consumption or EPA+DHA intake and age was included in the model, and a *P*-value for interaction <0.10 was considered statistically significant.

Results

Population characteristics

During 40 years of follow-up (mean survival age: 77 years), 348 of the 1373 men participating in the Zutphen Study died from CHD (**table 5.1**). Of these deaths, 66 where sudden coronary deaths (19% of all CHD deaths).

Among the men who were included in the study in 1960, the percentage of fish consumers varied between 71 and 81% between 1960 and 2000 (table 5.1) and average fish consumption ranged from 16 to 21 g per day. In all measurement rounds, lean fish was the major type of fish consumed (between 58 and 80% of the total fish consumption). Moreover, average EPA+DHA intake from fish varied between 136 and 236 mg per day in the period 1960-2000. Among those men who were newly included in the study in 1985, fish consumption and EPA+DHA intake from fish was comparable to the men who participated since 1960. The correlation between EPA+DHA intake from fish and total fish consumption ranged from 0.60 in 2000 to 0.80 in 1960.

Fish consumption, EPA+DHA intake and CHD death

Long-term, i.e. cumulative average, fish consumers –consuming on average 22 g per day– had a 27% lower CHD death risk (*P*-value: 0.16; **table 5.2**), while recent fish consumption was not associated with CHD death (data not shown).

For the associations between long-term fish consumption or EPA+DHA intake and CHD death, we found a significant and positive interaction with age, indicating that these associations were weaker at an older age (**figure 5.1A** and **B**). The HRs for long-term fish consumption compared with no fish consumption increased from 0.32 (95%CI: 0.13 to 0.80) at age 50 to 0.65 (0.42 to 1.02) at age 65 (*P*-value for interaction: 0.06, figure 5.1A). From age 70 onwards, the confidence intervals were too wide to draw conclusions from the reported associations. For long-term fatty-fish consumption, similar associations were observed (*P*-value for interaction: 0.06, figure 5.1A). In addition, we found an inverse association between EPA+DHA intake and CHD death among men with an intake below as well as above 250 mg per day compared with no intake (figure 5.1B). However, HRs were comparable with those for total fish consumption and no dose-response relationship was found (*P*-value for trend: 0.27; table 5.2). Adjustment for the prevalence of chronic disease, i.e. myocardial infarction, stroke and cancer, instead of the use of a serum cholesterol lowering diet slightly strengthened the associations between fish consumption and CHD death (data not shown).

Table 5.1. Characteristics of men participating in the Zutphen Study by year of measurement[1]

	Cohort	1960	1965	1970	1985	1990	1995	2000
Number of participants	*1960*	872	721	615	349	231	114	51
	1985	-	-	-	476	306	161	68
Cumulative number of deaths								
All coronary heart disease		-	13	40	176	231	297	348
Sudden coronary[2]		-	7	19	62	62	64	66
Age (years)[3]		49 ± 6	54 ± 5	59 ± 5	71 ± 5	75 ± 5	80 ± 4	83 ± 3
Fish users (%)	*1960*	81	76	71	73	74	76	78
	1985	-	-	-	72	75	78	81
Total fish consumption (g)	*1960*	20 ± 24	21 ± 24	18 ± 20	17 ± 19	16 ± 20	19 ± 19	21 ± 21
	1985	-	-	-	19 ± 26	16 ± 17	20 ± 22	22 ± 19
EPA+DHA intake from fish (mg)	*1960*	225 ± 419	236 ± 373	173 ± 235	142 ± 242	136 ± 220	188 ± 327	193 ± 280
	1985	-	-	-	173 ± 358	142 ± 204	193 ± 256	186 ± 231
Energy intake (kcal)		3107 ± 668	2965 ± 672	2599 ± 534	2240 ± 507	2102 ± 463	2104 ± 463	2073 ± 447
Alcohol intake (g)		4 ± 10	6 ± 11	9 ± 12	13 ± 17	10 ± 14	11 ± 14	12 ± 14
Wine users (%)		2	5	6	23	29	34	44
Saturated fat intake (g)		60 ± 17	61 ± 18	50 ± 14	43 ± 15	37 ± 13	38 ± 12	36 ± 13
***Trans* unsaturated fatty acid intake** (g)		24 ± 9	22 ± 10	15 ± 7	11 ± 6	7 ± 4	4 ± 2	3 ± 2
***Cis* polyunsaturated fat intake** (g)		21 ± 7	21 ± 8	20 ± 7	17 ± 8	17 ± 9	16 ± 8	16 ± 8
***Cis* monounsaturated fat intake** (g)		39 ± 12	42 ± 13	37 ± 10	27 ± 9	27 ± 8	27 ± 9	29 ± 9
Vegetable consumption (g)		201 ± 74	176 ± 69	181 ± 59	176 ± 72	162 ± 71	161 ± 62	131 ± 50
Fruit consumption (g)		112 ± 86	150 ± 109	168 ± 130	200 ± 141	234 ± 143	246 ± 150	254 ± 175

Table 5.1 continues on the next page.

Continuation of table 5.1

Cohort	**1960**	**1965**	**1970**	**1985**	**1990**	**1995**	**2000**
Serum cholesterol lowering diet (*n*)	2	11	9	15	11	1	1
Body mass index (kg/m2)	24.1 ± 2.7	24.9 ± 2.7	25.2 ± 2.8	25.5 ± 3.1	25.5 ± 3.2	25.3 ± 3.4	26.0 ± 3.3
Prevalence of diabetes mellitus (%)	1	2	2	6	10	14	16
Systolic blood pressure (mmHg)	143 ± 20	142 ± 18	147 ± 21	151 ± 21	150 ± 21	150 ± 21	146 ± 21
Type of smoking (%)[4]							
Never and long-term ex	6	6	9	26	50	60	72
Recent ex	6	11	15	31	17	16	14
Current cigarettes	74	61	53	30	23	18	6
Current cigars or pipes	14	21	23	13	10	6	8
Socioeconomic status (%)							
Manual workers	38	37	38	30	29	30	29
Non-manual workers	34	36	37	41	42	41	45
Small-business owners	21	20	19	19	19	14	15
Professionals	7	7	7	10	11	14	11

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; [1]Numbers represent means ± SD, unless indicated otherwise; [2]Sudden coronary deaths were defined as cases of sudden death with a high likelihood to be coronary, occurring within 2 h of onset of symptoms in diagnosed cases or in people with a past diagnosis of coronary heart disease; [3]Age is defined as age on 31 December, the year preceding the year of examination; [4]Never and long-term ex-smokers are defined as men who never smoked or stopped smoking ≥10 years ago. Recent ex-smokers are defined as men who stopped smoking <10 years ago.

Fish consumption, eicosapenaenoic acid+docosahexaenoic acid intake and sudden coronary death

Long-term, i.e. cumulative average, fatty-fish consumption –on average 7 g per day– lowered sudden coronary death risk by 54%, while no associations were found with total and lean fish consumption (table 5.2). Additional analysis showed that the inverse association between fatty-fish consumption and sudden coronary death was independent of total fish consumption (HR: 0.41 [95%CI: 0.23 to 0.73]). Although the association between EPA+DHA intake from fish and sudden coronary death was stronger among men with an intake above 250 mg than among those with an intake below 250 mg compared with no intake, no clear dose-response relationship was found (*P*-value for trend: 0.18; table 5.2). Adjustment for the prevalence of chronic disease instead of the use of a serum cholesterol lowering diet slightly attenuated the associations between fatty-fish consumption and sudden coronary death, but overall conclusions remained the same (data not shown).

The effects of long-term fish consumption and EPA+DHA intake on other CHD deaths were comparable to the effects on total CHD death (data not shown).

Discussion

In the present study, long-term, i.e. cumulative average, fish consumption –on average 22 g per day, i.e. 1-2 servings per week– was inversely associated with CHD death. The strength of this association decreased with increasing age and remained statistically significant until age 65. In addition, long-term fatty-fish consumption –on average 7 g per day– lowered the risk of sudden coronary death, independent of age. We observed no clear dose-response relationship of EPA+DHA intake from fish with (sudden) coronary death.

The major strength of this study was the collection of detailed information on usual dietary intake at each of seven examination rounds and on coronary death during 40 years of follow-up. This enabled us to study recent and long-term fish consumption and EPA+DHA intake from fish in relation to CHD death and sudden coronary death, and to study possible interactions with age. Besides, the detailed information on potential confounders made it possible to study the independent relationships of fish consumption and EPA+DHA intake from fish with mortality.

The present study also has some weaknesses. First, the number of sudden coronary deaths (66 events) observed in the Zutphen Study may have been too small to detect a dose-response relation for EPA+DHA intake. Second, to account for changes in product composition, time-specific food composition tables are needed to calculate nutrient intake over a longer period of time. However, as the digitally updated version of the Dutch food composition database from 1996 contains values of EPA and DHA in fish obtained with improved laboratory analyses compared with values reported earlier, we used this table to calculate EPA+DHA intake from fish in the period 1960-1995 (19;20). Third, since frying can affect a fish meal's fatty-acid composition and *trans* unsaturated fatty acids in frying fats may increase cardiovascular risk, Mozaffarian *et al.* (31) suggested that these factors should be taken into account when studying the associations of fish consumption with CHD death. In the present study, it was not possible to consider different methods of fish preparation. However, detailed information on usual food consumption and nutrient intake made it possible to study the independent effects of lean, which is mostly fried, and fatty-fish consumption and to adjust for *trans* unsaturated fatty

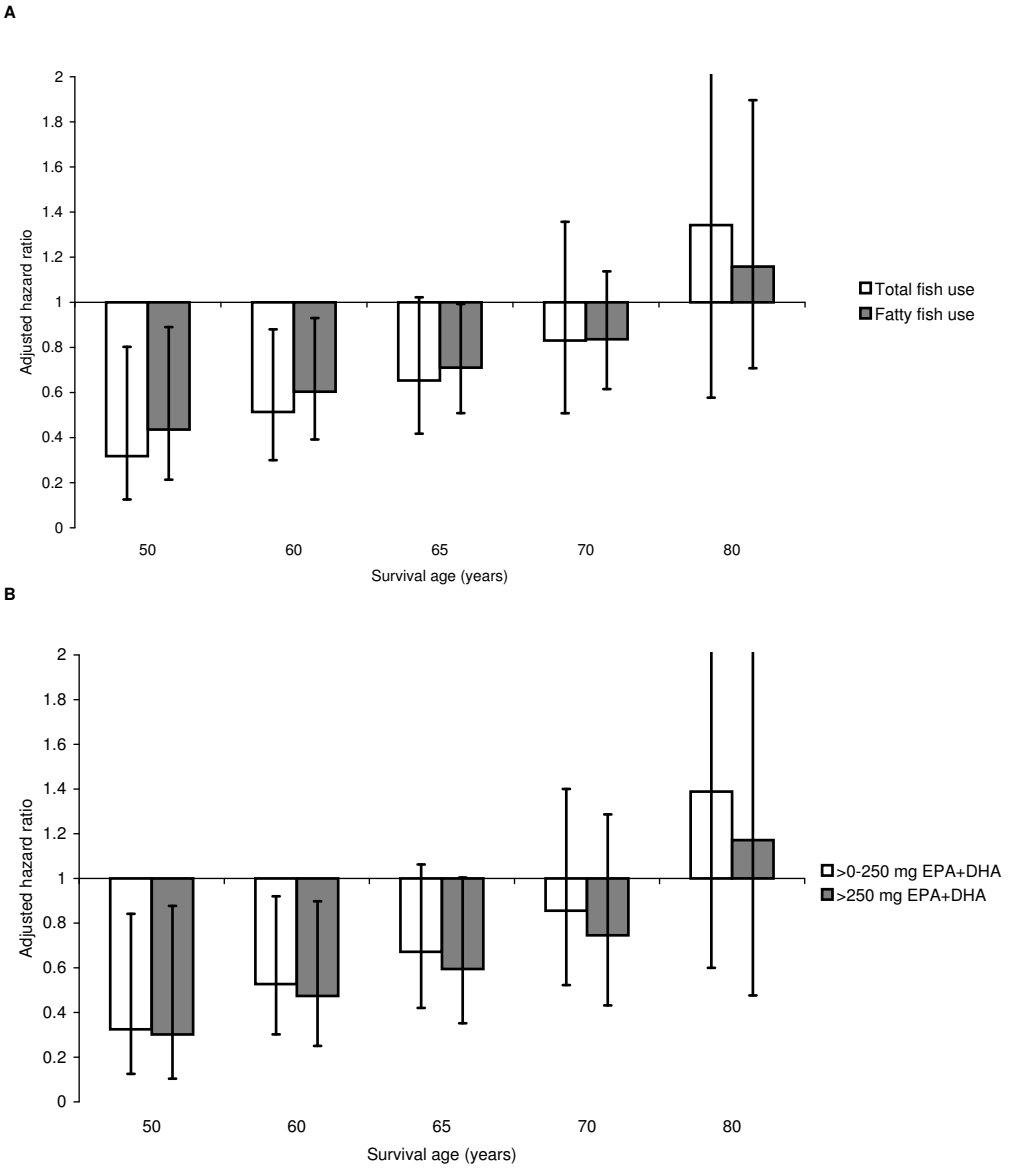

Figure 5.1. Hazard ratios, with 95% confidence intervals, for long-term fish consumption (A) and EPA+DHA intake from fish (B) in relation to coronary heart disease death at different ages and adjusted for energy intake, alcohol intake, wine use, fruit and vegetable consumption, saturated fat, *trans* unsaturated fatty acid, *cis* monounsaturated and *cis* polyunsaturated fat intake, serum cholesterol lowering diet, smoking, body mass index, prevalence of diabetes mellitus, systolic blood pressure, and socioeconomic status.

Table 5.2. Long-term fish consumption and EPA+DHA intake from fish in relation to 40-year coronary heart disease and sudden coronary death within the Zutphen Study

Exposure	Category	Coronary heart disease death				Sudden coronary death			
		HR[1]	**95% CI**	**HR[2]**	**95% CI**	**HR[1]**	**95% CI**	**HR[2]**	**95% CI**
Total fish consumption	No	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.70	0.46 to 1.06	0.73	0.47 to 1.13	0.94	0.37 to 2.36	0.89	0.34 to 2.30
Fatty fish consumption	No	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.87	0.64 to 1.16	0.88	0.65 to 1.19	0.44	0.27 to 0.74	0.46	0.27 to 0.78
Lean fish consumption	No	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.98	0.71 to 1.37	1.03	0.73 to 1.45	1.14	0.59 to 2.19	1.29	0.65 to 2.59
EPA+DHA intake	0 mg	1.00	-	1.00	-	1.00	-	1.00	-
	>0-250 mg	0.72	0.47 to 1.10	0.76	0.49 to 1.18	1.03	0.41 to 2.63	0.96	0.36 to 2.52
	>250 mg	0.64	0.40 to 1.02	0.65	0.40 to 1.06	0.72	0.26 to 2.05	0.68	0.23 to 2.02
	P-value for trend[3]		0.33		0.27		0.18		0.18

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; [1]Crude hazard ratios with 95% confidence limits (CI), HRs for fatty and lean fish are adjusted for each other; [2]HRs are additionally adjusted for energy intake, alcohol intake, wine use, fruit and vegetable consumption, saturated fat, *trans* unsaturated fatty acid, *cis* monounsaturated and polyunsaturated fat intake, serum cholesterol lowering diet, smoking, body mass index, prevalence of diabetes mellitus, systolic blood pressure, and socioeconomic status. Because of missing data in the covariates, the number of events is lower than the number mentioned in table 5.1, i.e. 336 coronary heart disease deaths and 63 sudden coronary deaths; [3]For EPA+DHA intake from fish, a *P*-value for trend was calculated using the continuously distributed variable.

acid intake. Fourth, for those men who were newly included in the study in 1985, information on fish consumption was missing in the period 1960-1970. By multiple imputations of fish consumption, EPA+DHA intake from fish, and other dietary covariates in 1960-1970, we were able to counter an underestimation of cumulative average intake from 1985 onwards for those men who were newly included in the study. However, assumptions that were made in the multiple imputation method may have led to less precise effect estimates. We repeated our analysis among the participants who were included in the study from 1960 (n = 875) and found similar associations between long-term fish consumption and (sudden) coronary death. Therefore, it is unlikely that the imputation of fish consumption, EPA+DHA intake, and other dietary covariates among those men who were newly included in the study from 1985 biased our results.

Our results confirm those from other prospective cohort studies that found an inverse association between fish consumption, EPA+DHA intake from fish and CHD death risk (31-36); however, significant inverse associations were only present until age 65. Compared with no intake, long-term EPA+DHA intake was associated with a lower CHD death risk among men with an intake below as well as above 250 mg per day and HRs were comparable. This confirms the findings from Mozaffarian *et al.* (5) who showed that a dose-response relationship between EPA+DHA intake from fish and CHD death is only present up to an intake of 250 mg per day, while intakes above 250 mg did not have a significant additional risk reduction.

Moreover, the present study showed that long-term fatty fish-consumption –on average 7 g per day– lowered the risk of sudden coronary death by 54% and confirms results from other prospective cohort studies (9;37). Results from two case-control studies suggest that there is a linear dose-response relation between blood or cell membrane levels of EPA and DHA, and sudden coronary death or cardiac arrest (11;12). In the present study, the association between EPA+DHA from fish and sudden coronary death was indeed stronger among men with an intake above 250 mg compared with the association among men with an intake below 250 mg; however, the trend was not statistically significant (P-value: 0.18). Lean fish consumption was not associated with sudden coronary death. Besides the difference in EPA and DHA content, fatty fish also has a higher content of other bioactive compounds such as vitamin D (21) than lean fish, which could have an additional beneficial effect. Furthermore, as already mentioned earlier, lean fish is mostly fried and although we adjusted for *trans* fatty acid intake, residual confounding cannot be ruled out.

Within the Zutphen population, average EPA+DHA intake from fish was ~200 mg per day. At this low level of intake, an anti-arrhythmic effect of EPA+DHA is the most likely explanation for the low risk of (sudden) coronary death (38). At low doses, an increase in circulating free EPA and DHA contributes to reducing arrhythmias by binding to the Na+ and L-type Ca+ channels in cell membranes. This inhibits the Na+ and L-type Ca+ currents in cell membranes, which prevent the generation of action potentials in injured cardiomyocytes (6;8;39).

The main conclusion of this study is that long-term fish consumption –on average 22 g per day– lowers the risk of CHD death, especially below age 65. Fatty-fish consumption lowers the risk of sudden coronary death. There is no clear dose-response relationship between EPA+DHA intake from fish and (sudden) coronary death.

Conflict of interest: For the Alpha Omega Trial, Daan Kromhout received grants from the Netherlands Heart Foundation and the National Institutes of Health (USA), and Unilever funded the production and distribution of the margarines, enriched with n-3 fatty acids, used in this trial.

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Chapter 6

Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study

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Abstract

Background: Little is known about the effects of dietary fiber intake on long-term mortality.

Objective: We aimed to study recent and long-term dietary fiber intake in relation to coronary heart disease and all-cause mortality.

Design: The effects of recent and long-term dietary fiber intakes on mortality were investigated in the Zutphen Study, a cohort of 1373 men born between 1900 and 1920, and examined repeatedly between 1960 and 2000. During that period, 1130 men died, 348 as a result of coronary heart disease. Hazard ratios were obtained from time-dependent Cox regression models.

Results: Every additional 10 g of recent dietary fiber intake per day reduced CHD mortality by 17% (95% CI: 2% to 30%) and all-cause mortality by 9% (0% to 18%). The strength of the association between long-term dietary fiber intake and all-cause mortality decreased from age 50 y (hazard ratio: 0.71 [95% CI: 0.55 to 0.93]) until age 80 y (0.99 [0.87 to 1.12]). We observed no clear associations for different types of dietary fiber.

Conclusions: A higher recent dietary fiber intake was associated with a lower risk of both coronary heart disease as well as all-cause mortality. For long-term intake, the strength of the association between dietary fiber and all-cause mortality decreased with increasing age.

Introduction

Epidemiological studies have shown that consumption of (whole-grain) cereals (1-4) and vegetables and fruit (5-8) may lower the risk of coronary heart disease (CHD) mortality. Dietary fiber is one of the components that may be responsible for the beneficial effects of these foods. Results from intervention trials have shown that (water-soluble) dietary fiber may lower blood cholesterol concentrations (9), reduce blood pressure (10;11), promote body-weight loss (12), and may improve insulin sensitivity (13) –thereby reducing the risk of CHD mortality (14-17). In a pooled analysis of cohort studies, total dietary fiber intake was inversely associated with the risk of CHD mortality. Furthermore, the intakes of dietary fiber from cereals or from fruits were inversely associated, independent of each other, with the risk of CHD mortality (14). However, little is known about the effects of long-term dietary fiber intake on all-cause mortality.

For prospective cohort studies in which dietary fiber intake is assessed only at baseline, consumption patterns and product composition are assumed to be constant over the entire study period. However, it is unlikely that exposure measurements in the past accurately reflect long-term dietary fiber intake, because consumption patterns change during the life-course. To obtain correct estimates of the long-term effects of dietary fiber intake, repeated measures and time-specific food-composition tables are needed (18;19). Moreover, the use of repeated measures, especially when a cumulative average method is used, reduces within-subject variation over time and, thereby, reduces misclassification of dietary fiber intake (20).

The objective of the present study is to investigate recent and long-term total dietary fiber intake and dietary fiber intake from various food groups in relation to CHD and all-cause mortality. For this purpose, we used up to 7 repeated measures of dietary fiber intake.

Subjects and methods

Study population

The Zutphen Study started as the Dutch contribution to the Seven Countries Study, a longitudinal study of the relations of diet and other risk factors with chronic diseases (21). The Zutphen Study has been carried out since 1960 among middle-aged men in Zutphen, an old industrial town (≈30 000 inhabitants) in the eastern part of the Netherlands. In 1960, a random sample was drawn of 1088 men born between 1900 and 1919 and residing for ≥5 y in Zutphen. Of those men, 878 participated in the Zutphen Study (response rate: 81%), and 872 took part in both dietary and physical examinations. The examinations were repeated in 1965 and 1970. In 1985, the group of 554 survivors was extended with a new random sample of men from the same birth cohort. Of the 1266 men who were invited, 939 men participated (response rate: 74%), and 825 men took part in both dietary and physical examinations. These examinations were repeated in 1990, 1995 and 2000.

Baseline data were collected in 1960 –i.e. before the Helsinki Declaration was developed– and oral informed consent was obtained in view of follow-up data. In 1985 and 1990, the study was approved by the Medical Ethics Committee of the University of Leiden (Leiden, Netherlands); in 1995 and 2000, the study was approved by the Medical Ethics Committee of the Netherlands Organisation for Applied Scientific Research (TNO).

Assessment of food consumption and dietary fiber intake

In all dietary surveys, information on habitual food consumption was collected by using the cross-check dietary history method (22), adapted to the usual Dutch diet (23;24). This method provides information about the participant's usual food consumption pattern in the period 6-12 mo before the interview. From 1985 on, the information about the usual food consumption pattern was limited to the month preceding the interview, because consumption patterns in 1985 were much more complicated those in the 1960s. The interviews were carried out by experienced dieticians in spring and early summer. Each participant was interviewed, in the presence of his wife if possible, about his usual food consumption on weekdays and weekends. On the basis of this daily pattern, average food consumption during a day or week (first check) and the quantity of foods bought per week (second check) were estimated, and those values were presented to the participants to calculate and verify their food consumption.

In the present study, dietary fiber is defined as constituents of plant cells that cannot be digested or absorbed in the human stomach and small intestine (25;26), particularly pectin, cellulose, hemicellulose, and lignin (27;28). The daily intakes of dietary fiber, total energy and other nutrients were calculated using time-specific food-composition tables to account for changes in product composition and for qualitative improvements in analytical methods (28-33). In addition, intakes of dietary fiber from bread and other cereal products, potatoes, legumes, fruits, and vegetables were calculated. Because the ratio of the interindividual and intraindividual variance in dietary fiber intake in the Zutphen Study was 2.1, the reproducibility of dietary fiber intake was relatively high (34).

Assessment of potential confounders

Detailed information on the type and amount of smoking was collected using standardized questionnaires (35). Information on alcohol intake and the use of a prescribed diet was obtained from the cross-check dietary history (23;24). During physical examinations, men's weight and height were measured, and body mass index (BMI; in kg/m^2) was calculated. Information about the prevalence of myocardial infarction, stroke, diabetes mellitus, and cancer was collected throughout the study. The men were classified into 4 levels of socioeconomic status according to occupation at baseline.

Case ascertainment

Participants were followed until death, or censored on June 30, 2000. Three participants were lost to follow-up during the study and were censored after their last physical examination. For each participant who died, the final allocation of the cause of death was done by a clinical epidemiologist (A Menotti, Association for Cardiac Research, Rome, Italy) and coded according to the Eight Revision of the International Classification of Diseases (36). Because the underlying cause of death in elderly persons is often difficult to ascertain, we included both primary and secondary causes of death in our analyses. CHD deaths, including cases of sudden death were codes 410-414.

Statistical analysis

Before analyses, intakes of dietary fiber and other nutrients were adjusted for total energy intake using the nutrient residual method (37). First, Cox proportional hazard analyses were

performed with age as the time variable, and information on dietary fiber intake was updated at each measurement round (called the most recent intake). Second, the cumulative average dietary fiber intake was used to better represent long-term intake (20). For those men who were newly included in the study in 1985, information on food consumption and dietary fiber intake was missing for the period from 1960 through 1970. Because average dietary fiber intake was lower in 1985 than in 1960-1970, taking cumulative averages excluding earlier intakes in the men included in 1985 would underestimate their intakes compared with those of the men included in 1960. To account for this underestimation, multiple imputation (5 times) (38) of dietary fiber intake and other dietary covariates from 1960 through 1970 was carried out among those men who were newly included in 1985, with the use of an adapted version of predicted mean matching (Lazzeroni *et al*., unpublished observations, 1990). The SAS code that was used for the multiple imputation can be downloaded (Internet: www.rivm.nl/sasmacros).

For Cox proportional hazard models the PHREG procedure of SAS/STAT software (version 9.1; SAS Institute, Inc, Carry, NC) was used. Hazard ratios (HRs) were calculated for every additional 10 g of energy-adjusted total dietary fiber intake and for energy-adjusted dietary fiber intake from bread and other cereal products, potatoes, legumes, vegetables, and fruit. The covariates in the model were total energy intake (kcal); *trans* unsaturated fatty acid, saturated fat and *cis* polyunsaturated fat intakes (nutrient residuals) (37); alcohol intake (indicator variables for 0, >0-20, >20 g/d); wine use (yes or no); fish intake (g/d); BMI (kg/m^2); cigar or pipe smoking (never or long-term former, recent former, or current) (35); cigarette smoking duration (divided by 10 y), the daily number of cigarettes smoked (divided by 10); use of a prescribed diet (yes or no); and baseline socioeconomic status (indicator variables for manual workers, non-manual workers, small-business owners and professionals). A possible interaction between dietary fiber intake and age was tested, and P for interaction <0.10 was considered statistically significant.

In the analyses for most recent intake, all covariates were updated at each measurement round, and all available data were used for the analyses. In the analyses for long-term intake, the cumulative average intake of all dietary covariates was updated at each measurement round. Nondietary covariates were updated with the most recent value at each measurement round. Because multiple imputations yielded 5 versions of the dataset, analyses of long-term dietary fiber intake were performed 5 times, and the results were pooled by using MIANALYZE in SAS/STAT.

Results

Population characteristics

During 40 y of follow-up (mean survival age: 77 y), 1130 of the 1373 men participating in the Zutphen Study died (**table 6.1**). A total of 348 men died of CHD.

Among the participants who were included in the study in 1960, average daily dietary fiber intake decreased remarkably –from 33 g/d in 1960 to 21 g/d among the survivors in 2000. In addition, average total energy intake decreased from 3107 kcal/d in 1960 to 2073 kcal/d in 2000. Consequently, average daily dietary fiber intake per 2500 kcal remained relatively constant during 40 y of follow-up (table 6.1). Among those men who were newly included in the study in 1985, the average daily intake of dietary fiber was comparable to that in men who started the study in 1960.

Table 6.1. Characteristics of men participating in the Zutphen Study by year of measurement[1]

	1960	**1965**	**1970**	**1985**	**1990**	**1995**	**2000**
Participants (*n*)							
1960 cohort	872	721	615	349	231	114	51
1985 cohort	-	-	-	476	306	161	68
Cumulative deaths (*n*)							
All-cause	-	40	103	412	645	889	1130
Coronary heart disease	-	13	40	176	231	297	348
Age (y)[2]	49 ± 6[3]	54 ± 5	59 ± 5	71 ± 5	75 ± 5	80 ± 4	83 ± 3
Total energy intake (kcal/d)	3107 ± 668	2965 ± 672	2599 ± 534	2240 ± 507	2102 ± 463	2104 ± 463	2073 ± 447
Dietary fiber intake (g/ 2,500 kcal/ d)							
1960 cohort	27 ± 7	24 ± 7	24 ± 6	28 ± 7	29 ± 8	28 ± 7	26 ± 6
1985 cohort	-	-	-	28 ± 8	29 ± 9	28 ± 7	26 ± 7
Alcohol intake (g/d)	4 ± 10	6 ± 11	9 ± 12	13 ± 17	10 ± 14	11 ± 14	12 ± 14
Wine users (%)	2	5	6	23	29	34	44
BMI (kg/m2)	24.1 ± 2.7	24.9 ± 2.7	25.2 ± 2.8	25.5 ± 3.1	25.5 ± 3.2	25.3 ± 3.4	26.0 ± 3.3
Overall smoking (%)[4]							
Never and long-term former smoker	6	6	9	26	50	60	72
Recent former smoker	6	11	15	31	17	16	14
Cigarette smoker	74	61	53	30	23	18	6
Cigars or pipes (or both) smoker	14	21	23	13	10	6	7

[1]*n* = 1373; [2]Defined as the subject's age on December 31st of the year preceding the year of examination; [3]Means ± SD (all such values); [4]Never and long-term former smokers are defined as subjects who never smoked or stopped smoking ≥10 y previously. Recent former smokers are defined as subjects who stopped smoking <10 y previously.

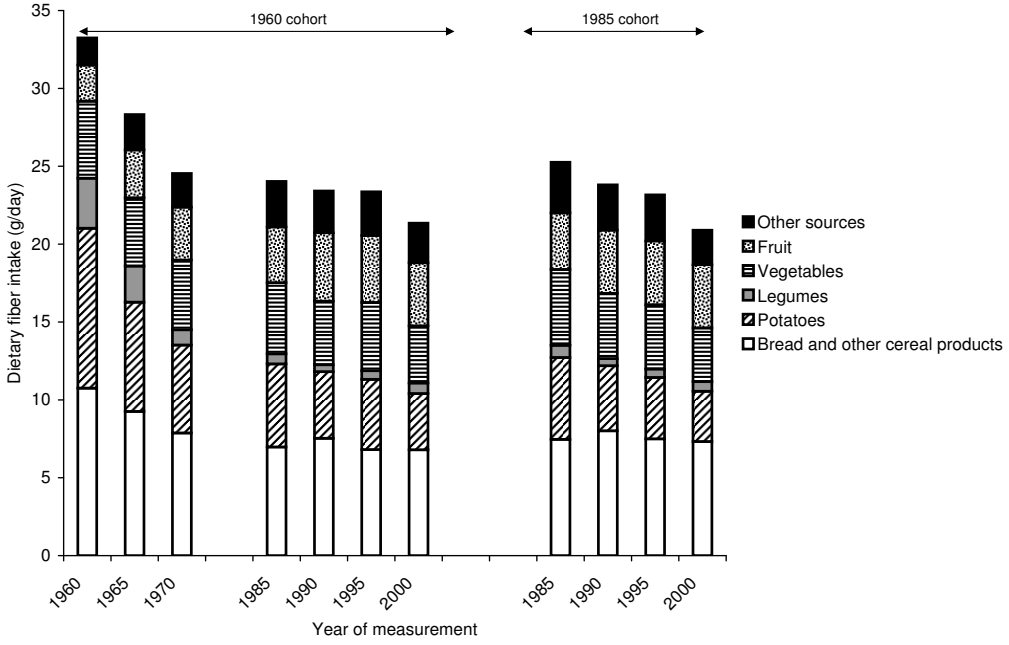

Figure 6.1. Changes in dietary fiber intake from various sources within the Zutphen Study (n = 1373) during 40 y of follow-up.

Bread and other cereal products were the major source of total dietary fiber intake (between 29% and 34% of total dietary fiber intake) in all survey rounds (**figure 6.1**). Total dietary fiber intake was most strongly correlated with dietary fiber intake from bread and other cereal products; correlation coefficients varied between 0.65 in 1995 and 0.78 in 1970.

Dietary fiber intake and mortality

After adjustment for potential confounders, every additional 10 g of recent dietary fiber intake was inversely associated with CHD (HR: 0.83 [95%CI: 0.70 to 0.98]; **table 6.2**) and all-cause mortality (0.91 [0.82 to 1.00]; **table 6.3**). In crude analyses, every additional 10 g of long-term dietary fiber intake was inversely associated with all-cause mortality. However, adjustment for potential confounders attenuated this association, and the HR increased from 0.88 (0.79 to 0.98) to 0.93 (0.83 to 1.04) (table 6.3).

For the association between long-term dietary fiber intake and all-cause mortality, we observed a significant and positive interaction with age (P = 0.03), which indicated that these associations weaken at a greater age. For all-cause death, the HR for every additional 10 g of long-term dietary fiber intake increased from 0.71 (0.55 to 0.93) at age 50 y to 0.99 (0.87 to 1.12) at age 80 y (**figure 6.2**). For CHD mortality, the increase in HRs was comparable, but the associations were not statistically significant (figure 6.2). We did not observe clear differences in the effects of dietary fiber from various sources on either CHD (table 6.2) or all-cause mortality (table 6.3).

Table 6.2. Recent and long-term energy-adjusted dietary fiber intake in relation to 40-y coronary heart disease (CHD) mortality (348 events) within the Zutphen Study[1]

	Recent intake[2]				Long-term intake[3]			
	Crude		Adjusted		Crude		Adjusted	
Dietary fiber intake	**HR**	**95% CI**	**HR[4,5]**	**95% CI**	**HR**	**95% CI**	**HR[4,5]**	**95% CI**
Total dietary fiber (per 10-g/d increment)	0.87	0.74 to 1.02	0.83	0.70 to 0.98	0.91	0.75 to 1.11	0.87	0.71 to 1.07
Dietary fiber (per 10-g/d increment)								
From bread and other cereal products	0.85	0.66 to 1.10	0.84	0.64 to 1.10	0.85	0.65 to 1.11	0.86	0.64 to 1.15
From potatoes	0.84	0.58 to 1.22	0.71	0.48 to 1.06	1.09	0.72 to 1.65	0.94	0.62 to 1.45
From legumes	0.64	0.34 to 1.20	0.64	0.34 to 1.20	0.54	0.25 to 1.15	0.52	0.25 to 1.09
From vegetables	1.02	0.55 to 1.89	0.88	0.48 to 1.65	1.29	0.46 to 3.64	1.00	0.36 to 2.77
From fruit	1.12	0.76 to 1.65	1.13	0.75 to 1.70	0.89	0.36 to 2.22	1.01	0.43 to 2.36

[1] n = 1373. HR, hazard ratio, obtained from time-dependent Cox proportional hazard models. Dietary fiber intake was adjusted for total energy intake by using the nutrient residual method (37); [2]Dietary fiber intake and all covariates were updated at each measurement round; [3]The updated cumulative average intake of all dietary covariates was used. Non-dietary covariates were updated with most recent values at each measurement round; [4]HRs were adjusted for total energy, saturated fat, *trans* unsaturated fatty acid and *cis* polyunsaturated fat intakes; alcohol intake; wine use; fish intake; prescribed diet; the number of cigarettes smoked; the duration of cigarette smoking; cigar or pipe smoking; BMI; and socioeconomic status; [5]Because of missing data in the covariates, the number of events was less than 348 –i.e. 336 CHD deaths.

Table 6.3. Recent and long-term energy-adjusted dietary fiber intake in relation to 40-y all-cause mortality (1130 events) within the Zutphen Study[1]

	Recent intake[2]				Long-term intake[3]			
	Crude		Adjusted		Crude		Adjusted	
Dietary fiber intake	**HR**	**95% CI**	**HR[4,5]**	**95% CI**	**HR**	**95% CI**	**HR[4,5]**	**95% CI**
Total dietary fiber (per 10-g/d increment)	0.89	0.81 to 0.97	0.91	0.82 to 1.00	0.88	0.79 to 0.98	0.93	0.83 to 1.04
Dietary fiber (per 10-g/d increment)								
From bread and other cereal products	0.88	0.76 to 1.02	0.92	0.79 to 1.07	0.80	0.69 to 0.94	0.90	0.77 to 1.05
From potatoes	1.05	0.86 to 1.29	0.95	0.77 to 1.19	1.09	0.86 to 1.39	1.06	0.85 to 1.34
From legumes	0.98	0.71 to 1.35	0.83	0.60 to 1.15	1.02	0.67 to 1.55	0.91	0.61 to 1.34
From vegetables	0.94	0.66 to 1.32	0.91	0.64 to 1.29	0.88	0.47 to 1.66	0.86	0.45 to 1.63
From fruit	0.78	0.62 to 0.99	0.94	0.74 to 1.21	0.57	0.36 to 0.91	0.77	0.49 to 1.20

[1] n = 1373. HR, hazard ratio, obtained from time-dependent Cox proportional hazard models. Dietary fiber intake was adjusted for total energy intake by using the nutrient residual method (37); [2]Dietary fiber intake and all covariates were updated at each measurement round; [3]The updated cumulative average intake of all dietary covariates was used. Non-dietary covariates were updated with most recent values at each measurement round; [4]HRs were adjusted for total energy, saturated fat, *trans* unsaturated fatty acid and *cis* polyunsaturated fat intakes; alcohol intake; wine use; fish intake; prescribed diet; the number of cigarettes smoked; the duration of cigarette smoking; cigar or pipe smoking; BMI; and socioeconomic status; [5]Because of missing data in the covariates, the number of events was less than 1130 –i.e. 1048 all-cause deaths.

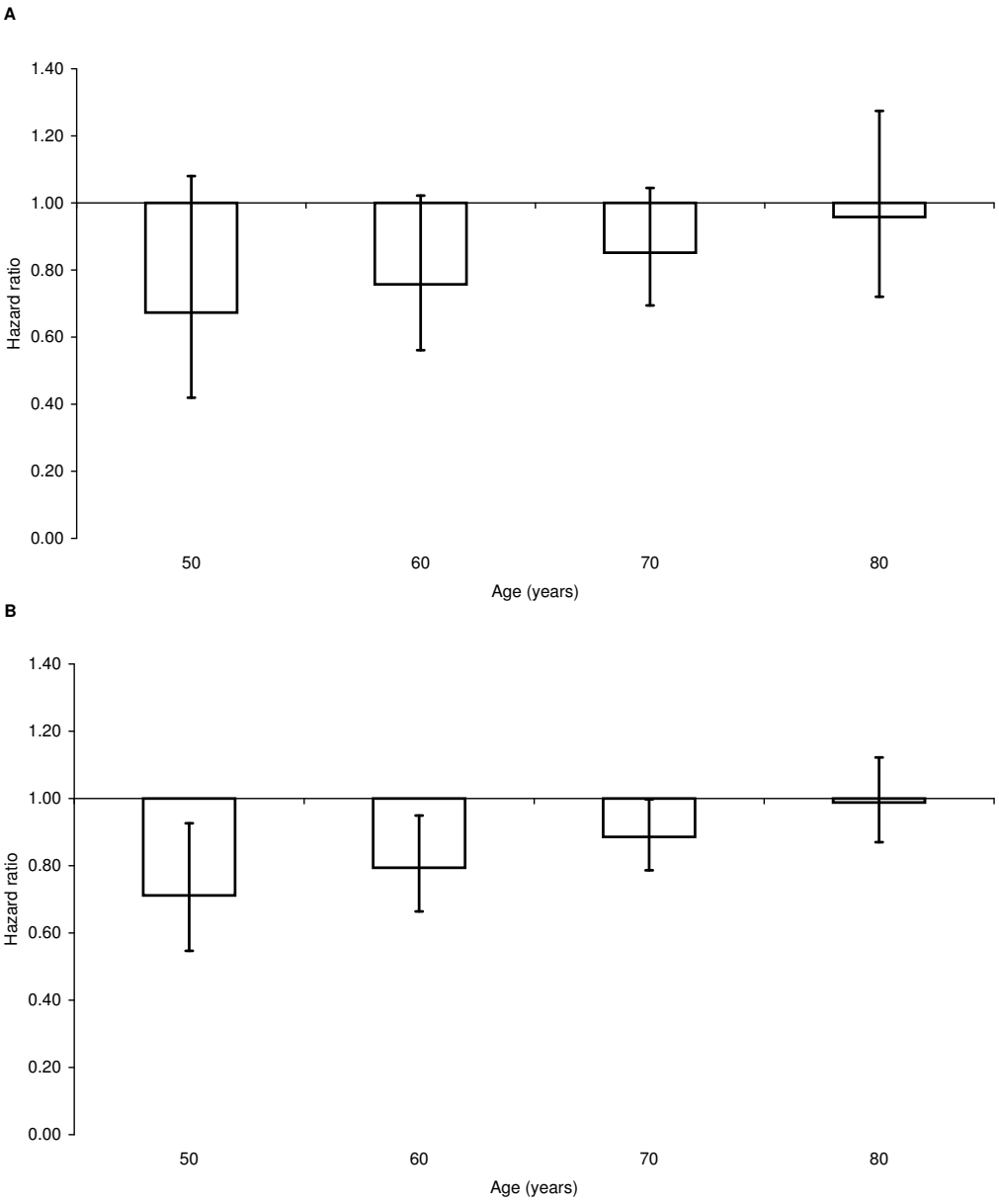

Figure 6.2. Adjusted hazard ratios (and 95% CIs) at different ages, obtained from time-dependent Cox proportional hazard models, for every additional 10 g of long-term energy-adjusted dietary fiber intake (by using the nutrient residual method) (37) in relation to 40-y coronary heart disease (A; n = 336) and all-cause (B; n = 1048) mortality within the Zutphen Study (n = 1373). Hazard ratios were adjusted for total energy, saturated fat, *trans* unsaturated fatty acid and *cis* polyunsaturated fat intakes; alcohol intake; wine use; fish intake; prescribed diet; the number of cigarettes smoked; duration of cigarette smoking; cigar or pipe smoking; BMI; and socioeconomic status. P for interaction with age = 0.26 for coronary heart disease mortality and 0.03 for all-cause mortality. Because of missing data in the covariates, the number of events was less than that mentioned in table 6.1.

Discussion

In the present study, recent dietary fiber intake was inversely associated with both CHD and all-cause mortality. For long-term intake, the strength of the associations between dietary fiber and all-cause mortality decreased with increasing age. We observed no clear differences in the effect of dietary fiber intake from various food groups on mortality.

The major strength of the present study was the collection of detailed information on usual dietary intake at each of 7 examination rounds and on coronary death during 40 y of follow-up. This enabled us to study recent and long-term –i.e. cumulative average– dietary fiber intakes in relation to coronary and all-cause mortality and to study a possible interaction with age. The detailed information on potential confounders made it possible to study the independent relations of (various sources of) dietary fiber intake with mortality.

The present study also has some weaknesses. First, for those men who were newly included in the study in 1985, information about dietary fiber intake was missing for the period of 1960 to 1970. By multiple imputation (38) of dietary fiber intake and other dietary covariates in 1960-1970, we were able to counter an underestimation of cumulative average intake from 1985 for those men who were newly included in the study. However, the assumptions that were made in the multiple imputation method may have led to less precise effect estimates. Without imputation of dietary fiber intake and other dietary covariates, the associations between long-term dietary fiber intake and mortality were slightly attenuated, but the overall conclusions remained the same. Therefore, it is unlikely that bias occurred. Second, information on physical activity was not collected continuously during the whole follow-up period and therefore was not available for the present study. Adjustment for total energy intake per kg body weight as a proxy for physical activity (39) did not change our results.

Our results confirm those from large prospective cohort studies that found an inverse association between dietary fiber intake and CHD mortality (40-42). Pereira *et al.* (14) conducted a pooled analysis of 10 cohort studies from the United States and Europe and estimated that every additional 10 g of dietary fiber/d reduced CHD mortality risk by 19%. We found a similar association of recent dietary fiber intake and CHD mortality. In the pooled analysis of Pereira *et al.* (14), this association became stronger (HR: 0.73 [95%CI: 0.61 to 0.87]) after adjustment for measurement error (by using the regression calibration method) in dietary fiber intake. In the present study, the cumulative average dietary fiber intake was used not only to better represent long-term intake but also to reduce measurement error by reducing the within-subject variation of dietary fiber intake over time (20). Until age 70 y, the effects of cumulative average dietary fiber intake on CHD mortality were indeed stronger than those of recent intake; however, the observed associations were not statistically significant.

Moreover, Pereira *et al.* (14) observed that dietary fiber intakes from cereals or from fruit were, independent of each other, inversely associated with the risk of CHD mortality. Every additional 10 g of dietary fiber intake from cereals lowered CHD mortality risk by 29%, and that of dietary fiber from fruit lowered CHD mortality risk by 35%. In the present study, we did not observe a clear difference between the effects of dietary fiber from various sources on CHD mortality. Because total dietary fiber intake was inversely associated with mortality, the intake of all types of fiber-rich foods should be encouraged.

Several mechanisms have been proposed by which dietary fiber may reduce CHD mortality risk (16). Soluble fibers increase the rate of bile acid excretion by binding bile acids in the small

intestine, thereby reducing serum total and LDL cholesterol (43-45). In the large intestine, soluble fibers are fermented by bacteria. One of the by-products of this process is short-chain fatty acids. Hepatocytes, when exposed to these short-chain fatty acids, may increase glucose oxidation, decrease free fatty acid release and insulin clearance, and improve insulin sensitivity (46;47). The increase in insulin sensitivity results in lower circulating insulin concentrations, an effect that has been shown to reduce blood pressure (48). Moreover, the short-chain fatty acids inhibit cholesterol synthesis by limiting the action of 3-hydroxy-3-metylglutaryl-coenzyme A reductase (46). The effects of dietary fiber on LDL cholesterol, insulin sensitivity, and blood pressure may explain the inverse association between dietary fiber intake and CHD mortality. In the present study, the associations between dietary fiber intake and mortality were stronger for recent intake than for long-term intake. Moreover, the effects of long-term dietary fiber were stronger at younger ages –in other words, when dietary fiber intake was calculated over a shorter period of time. This finding suggests that the mechanisms by which dietary fiber may reduce mortality are primarily short-term effects.

Besides the inverse association between dietary fiber intake and CHD mortality, we observed a significant and inverse association with all-cause mortality, which confirmed the results from Todd *et al.* (49) and Kromhout *et al.* (50). However, for long-term dietary fiber intake, an inverse association with all-cause mortality was present only until age 70 y. Because the effects on all-cause mortality were less strong than those on CHD mortality, the inverse association between dietary fiber intake and all-cause mortality is mainly explained by the inverse association with CHD mortality.

In conclusion, recent dietary fiber intake was inversely associated with CHD and all-cause mortality risk. For long-term intake, the strength of the associations between dietary fiber and all-cause mortality decreased with increasing age. Differences between the effects of various sources of dietary fiber on mortality were not observed.

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Chapter 7

General Discussion

The main objective of this thesis was to assess the relationships between recent and long-term exposure to known lifestyle and dietary risk factors, and cardiovascular mortality among men participating in the Zutphen Study. For this purpose, we used up to seven repeated measures of lifestyle factors and dietary habits in the period 1960-2000. In addition to hazard ratios, we presented some of our results in terms of differences in life expectancy at age 50.

Main findings

The main findings of the studies described in this thesis are summarized in **table 7.1** and **7.2**. Within the Zutphen Study, we found that both the number of cigarettes smoked and smoking duration were strongly associated with mortality risk (chapter 2). Long-term cigarette smoking decreased life expectancy by about 7 years and exclusive cigar or pipe smoking decreased life expectancy by about 5 years. Stopping smoking cigarettes at age 50 increased life expectancy by 3.3 years. Furthermore, we observed that long-term light alcohol intake lowered cardiovascular and all-cause mortality risk (chapter 3). Compared to men who do not consume alcohol, light wine consumers had a 5 years longer life expectancy. Next, we showed that average *trans* unsaturated fatty acid intake in the Zutphen Study decreased from 7 to about 1 percent of energy intake between 1960 and 2000 (chapter 4) and that long-term *trans* unsaturated fatty acid intake was positively associated with sudden coronary death. In contrast, long-term fatty fish consumption was inversely associated with sudden coronary death (chapter 5). The strength of the association between long-term total fish consumption and coronary heart disease (CHD) death decreased with increasing age. We observed no clear dose-response relationship between the intake of the n-3 fatty acids EPA+DHA and (sudden) coronary death. Finally, we found that a higher recent dietary fiber intake was associated with a lower risk of both CHD as well as all-cause mortality (chapter 6).

Methodological considerations

The Zutphen cohort

The Dutch contribution to the Seven Countries Study, the Zutphen Study, has been carried out since 1960 among middle-aged men. Zutphen is an old industrial town in the eastern part of the Netherlands with about 30 000 inhabitants. In 1960, a 4/9 statistical sample was drawn from all men born between 1900 and 1919 and residing at least 5 years in Zutphen (n = 1088). Of those men, 878 participated in the Zutphen Study (response rate: 81%). Examinations were repeated in 1965, 1970, 1985, 1990, 1995 and 2000. In 1985, the group of 554 survivors was extended with a new random sample of men of the same birth cohort. Of the 1266 men who were invited in 1985, 939 men participated (response rate: 74%). In total 1437 men participated in the Zutphen Study. In every examination round, the participants that took part in both the dietary and physical examinations were selected for the studies described in this thesis (n = 1373).

Extending the 1960 cohort with a new random sample of men in 1985 increased the power of the study, but it also has a major limitation. For those men who were newly included in the Zutphen Study from 1985, information on lifestyle factors and food consumption was missing from 1960 through 1970. Within the Zutphen Study, we observed that average alcohol intake

Table 7.1. Relationships of long-term exposure to lifestyle factors with cardiovascular mortality and life expectancy within the Zutphen Study

Ch	Lifestyle factor	Unit	HR CVD mortality (95% CI)	HR all-cause mortality (95% CI)	Differences in LE at age 50 (95% CI)
2	No. of cigarettes smoked	per 10 cigarettes per day	1.06 (0.93 to 1.20)	1.11 (1.01 to 1.21)	n.a.
	Duration of cigarette smoking	per 10 years	1.15 (1.07 to 1.23)	1.12 (1.06 to 1.18)	n.a.
	Cigarette smoking	current *versus* never or long-term former cigarette smoker	1.66 (1.35 to 2.03)	1.60 (1.38 to 1.86)	-6.8 years[1] (-9.3 to -4.3 years)
	Exclusive cigar or pipe smoking	current *versus* never or long-term former cigar or pipe smoker	n.a.	n.a.	-4.7 years[1] (-8.0 to -1.5 years)
	Stopping smoking cigarettes at age 50		n.a.	n.a.	3.3 years[2] (1.9 to 4.7 years)
3	Total alcohol intake	≤20 grams per day *versus* 0 gram per day	0.70 (0.55 to 0.89)	0.75 (0.63 to 0.91)	2.3 years (0.05 to 4.2 years)
	Alcohol intake from wine	≤20 grams per day *versus* 0 gram per day	0.68 (0.53 to 0.86)	0.73 (0.62 to 0.87)	4.7 years[3] (1.6 to 7.7)

HR: hazards ratio, CI: confidence interval, CVD: cardiovascular diseases, LE: life expectancy, n.a.: not assessed; [1]Difference in life expectancy was calculated for, respectively, current cigarette smokers and exclusive cigar or pipe smokers compared to never of long-term former overall smokers; [2]Difference in life expectancy was calculated compared to men who continued smoking at that age; [3]Difference in life expectancy was calculated for those men who consumed wine (>0 gram per day) compared to those who do not consume alcoholic beverages.

Table 7.2. Relationships among dietary factors and (sudden) coronary mortality within the Zutphen Study

Ch	Dietary factor	Unit	HR CHD mortality (95% CI)	HR sudden coronary mortality (95% CI)
		Long-term exposure		
4	*Trans* unsaturated fatty acids	per 2% of energy intake per day	1.01 (0.82 to 1.24)	1.62 (1.01 to 2.60)
5	Total fish	yes *versus* no	0.73 (0.47 to 1.13)[1]	0.89 (0.34 to 2.30)
	Fatty fish	yes *versus* no	0.88 (0.65 to 1.19)[1]	0.46 (0.27 to 0.78)
		Recent exposure		
6	Dietary fiber	per 10 grams per day[2]	0.83 (0.70 to 0.98)	n.a.

HR: hazards ratio, CI: confidence interval, CHD: coronary heart disease, n.a.: not assessed; [1]A significant interaction with age was observed. For total fish consumption, the HRs decreased from 0.32 (0.13 to 0.80) at age 50 to 1.34 (0.58 to 3.12) at age 80. For fatty fish, the HRs were comparable with the HR for total fish consumption; [2]Energy adjusted using the nutrient residual method.

was higher in 1985 than in 1960-1970 (chapter 3). Calculating long-term, i.e. cumulative average, alcohol intake ignoring earlier intakes in those men who were newly in the study in 1985 would overestimate their intake compared with men included in 1960. In contrast, average *trans* unsaturated fatty acid intake was lower in 1985 than in 1960-1970 (chapter 4) and the use of cumulative averages ignoring earlier intakes in those men who were newly included in the study in 1985 would underestimate their intakes as compared with those of men included in 1960. To account for this over- or underestimation, multiple imputation (5 times) (1) of the dietary exposure variables and other dietary covariates between 1960 through 1970 was carried out among those men who were newly included in 1985, with an adapted version of predicted mean matching (2). For each missing observation, the nearest –in terms of predicted value– non-missing observation was drawn and assigned as the imputed value to the missing observation. The variables, besides the dietary covariates, that were used to impute the missing observations were age at start and end of follow-up, and indicator variables for the outcome. The SAS code that was used for the multiple imputation can be downloaded from www.rivm.nl/sasmacros. Analyses on long-term, i.e. cumulative average, exposure were performed on five imputed datasets and results were pooled using the MIANALYZE procedure of SAS/STAT software. To check whether the multiple imputation method did not bias our results, we repeated all our analyses without the imputation. Although the effect estimates changed slightly, overall conclusions remained the same.

Long-term exposure

The main objective of this thesis was to compare the effects of most recent exposure with the effects of long-term exposure to known lifestyle and dietary factors on mortality. For most recent exposure, information on lifestyle factors and dietary intake was updated at each measurement round. In other words, exposure between 1960 and 1965 was calculated from lifestyle factors and dietary intake from the 1960 examination round; exposure between 1965 and 1970 was calculated from lifestyle factors and dietary intake from the 1965 measurement round, and so on. To better represent long-term exposure, we calculated cumulative averages. With this method, exposure between 1960 and 1965 was calculated from lifestyle factors and dietary intake from the 1960 examination round; exposure between 1965 and 1970 calculated from the *average* exposure to lifestyle and dietary factors from the 1960 and 1965 examination rounds, and so on (3). Averaging repeated measures reduces within-subject variation over time and, thereby, reduces measurement error (3;4). For example, average *trans* unsaturated fatty acid intake in the Zutphen Study decreased from 7 to about 1 percent of total energy intake during 40 years of follow-up (chapter 4) and the correlation between the first two measurement rounds was 0.4 compared to 0.3 between the last two measurement rounds. For a measurement with an intra class correlation of 0.3, the ratio of between-subject and within-subject variation is 1:2.33, yielding a attenuation coefficient of 0.46 (**table 7.3**). This means that the regression coefficient observed when fitting a model on the observed exposures, will be 0.46 of the true regression coefficient between the exposure and the outcome. For example, an observed regression coefficient of 0.41 –which corresponds to a HR of 1.50– will attenuate to 0.19 (0.41*0.46; corresponding HR: 1.21) when taking the attenuation coefficient into account. By averaging, for example, 4 measurements, the ratio of between-subject and within-subject variation changes to 1:(2.33/4) and results in an attenuation coefficient of 0.63 (table 7.3).

The more repeated measures, the lower the within-subject variation which results in higher attenuation coefficients. This indicates that the long-term, i.e. cumulative average, exposure will yield regression coefficients that are closer to the true coefficients.

Table 7.3. Improvement of the validity of a measurement by averaging k repeated measures

Intra class correlation[1]	Attenuation coefficients[2]					
	k=2	k=3	k=4	k=5	k=6	k=7
0.10	0.18	0.25	0.31	0.36	0.40	0.44
0.20	0.33	0.43	0.50	0.56	0.60	0.64
0.30	0.46	0.56	0.63	0.68	0.72	0.75
0.40	0.57	0.67	0.73	0.77	0.80	0.82
0.50	0.67	0.75	0.80	0.83	0.86	0.88
0.60	0.75	0.82	0.86	0.88	0.90	0.91
0.70	0.82	0.88	0.90	0.92	0.93	0.94
0.80	0.89	0.92	0.94	0.95	0.96	0.97
0.90	0.95	0.96	0.97	0.98	0.98	0.98

[1]The intra class correlations are defined as the between-subject variation divided by the sum of between-subject and within-subject variation; [2]The attenuation coefficients are calculated from the intra class correlation coefficients by dividing the within-subject variation by the number of measurements.

The use of repeated measures may also give more insight into the etiology of diseases. With the exception of dietary fiber intake, the effects of long-term exposure to the known lifestyle and dietary factors on mortality were stronger than those of recent exposure. This suggests that long-term exposure is etiologically more relevant than most recent exposure. However, this can not be concluded with certainty because it is not possible to separate the effects of reduction in measurement error from the truly stronger etiologic relationship with long-term exposure than with recent exposure. Hu *et al.* also observed stronger effects of the cumulative average exposure on CHD than of baseline or recent exposure (3) and recognize the fact that this method can not separate the effects of reduced measurement error from etiological relevance. On the other hand, a stronger effect of recent exposure, such as for dietary fiber intake (chapter 6), indicates real etiological relevance of recent rather than long-term exposure, as this can not be explained by the effects of measurement error. In line with Hu *et al.* (3), we feel that there are probably other sensible ways to update diet that need to be explored in further research.

The use of a cumulative average exposure is only one aspect of reducing measurement error in the assessment of long-term exposure to lifestyle and dietary habits, namely the reduction in within-subject variation. Furthermore, it is important to perform repeated measures of lifestyle and dietary habits over a longer period of time to take into account changes in these habits during the course of life. In the Zutphen Study, information on lifestyle and dietary habits was collected seven times during 40 years of follow-up. In principle, the data was collected every five years; however, not in the period from 1970 through 1985. Finally, the use of repeated measures of lifestyle and dietary habits does not reduce the systematic measurement error of the method used for collecting these data, i.e. the respondent specific bias in self-reported lifestyle and dietary habits. Therefore, the additional use of biomarkers of lifestyle and dietary habits when assessing the exposure to lifestyle and dietary habits is recommended (5).

Sudden death

In the Zutphen Study, sudden death was defined as death within 2 hours after the onset of symptoms. Men who died suddenly with a past diagnosis of CHD or with symptoms likely to be coronary were classified as sudden coronary deaths. Other cases of sudden death had a low likelihood to be coronary. In the present study, 60% of the sudden death cases were of coronary origin. Goraya *et al.* (6) found in the Olmsted County population of men above the age of 25, that about 50% of all sudden cardiac deaths had a prior diagnosis of CHD.

Because the risk of atherosclerotic coronary disease increases with age, the risk of sudden death is also expected to increase with age. However, most of the sudden coronary deaths in the Zutphen Study occurred before the 1985 measurement round, i.e. when the men were relatively young. At an older age, the probability of dying from multiple causes increases. In that case, competing causes of death decrease the probability that sudden coronary death will be the primary cause of death.

In the Zutphen Study, all sudden coronary deaths occurred among the men who were included in the study in 1960. As a consequence, the inclusion of a new random sample of men from the same birth cohort in 1985 was not necessary for analyses on this endpoint. Therefore, we repeated our analyses on the sudden coronary death among the men who started the study from 1960. For both *trans* unsaturated fatty acids (chapter 4) and (fatty) fish consumption (chapter 5), the overall conclusions did not change.

Age as time-variable

In the analyses on epidemiological cohort data, time between the first examination round and the event or end of follow-up is generally used. In the studies described in this thesis, age was used as the time-variable. Time at entry was age on December 31st of the year preceding the year the men participated in both the dietary and physical examinations for the first time, i.e. the first measurement round; exit time was age when the participants died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. By using age as the time variable, the hazard function can be directly interpreted as the age-specific incidence function (7;8). Moreover, since age is taken into account in the non-parametric term of the hazard function, age is most effectively controlled for (7;8).

To test whether the observed associations were constant over age (our time-variable), we included a product term between the exposure variable of concern and age in our models and a *P*-value for interaction <0.10 was considered significant. We found that the inverse association between long-term fish consumption and CHD mortality (chapter 5), and the inverse association between long-term dietary fiber intake and all-cause mortality (chapter 6) weakened with increasing age. These findings suggest that beneficial effects of both long-term fish consumption and long-term dietary fiber intake may be restricted to men until age 70. However, from age 70 onwards, the confidence intervals were too wide to draw conclusions from the reported associations.

Confounding

Socioeconomic status

There is consistent evidence for an inverse relationship between different indicators of socioeconomic status and cardiovascular diseases (9;10). Traditional indicators of socioeconomic

status include occupation, education and income (9;11). Data on socioeconomic status was not collected continuously at each measurement round of the Zutphen Study. Therefore, we used baseline occupation as an indicator of socioeconomic status. Occupation forms a structural link between education and income and it provides a measure of environmental and working conditions, latitude in decision-making, and physical demands of the job (11). On the other hand, occupational classes are comprised of heterogeneous occupations with substantial variation in education, income and prestige. Furthermore, it is difficult to classify those who work at home or those who are retired (11). For those men who started in the Zutphen Study in 1960, average age was 49 years and only a few men will have changed their jobs during follow-up but retired instead. In 1985, when the men were between 65 and 84 years of age, only a small number of participants indicated to have a paid job and information on the longest held occupation was collected. The information on socioeconomic status from 1960 and 1985 showed substantial agreement (Cohen's kappa: 0.61). So, the men were already in a late phase in their careers at the start of the study and we considered baseline occupation a good indicator of socioeconomic status during the follow-up period.

Occupation, education and income appear to be independently of each other related to dietary habits (12;13). As reviewed by Darmon *et al.*, people with a higher socioeconomic status tend to consume more whole grains, lean meats, fish, low-fat dairy products, vegetables and fruits, while the consumption of refined grains and added fats has been associated with lower socioeconomic status (14). Moreover, Nielsen *et al.* indicated that effect of specific alcohol beverages, especially wine, on mortality may be restricted to certain socioeconomic classes (15). In the Zutphen Study, the increase in the percentage of wine users during follow-up was observed in all levels of socioeconomic status. Among manual workers, the percentage of wine users increased from 0% in 1960 to 41% in 2000; among professionals, the percentage of wine users increased from 13% to 85%. Moreover, stratified analyses showed that the inverse association between wine consumption and mortality was present in all socioeconomic classes (chapter 3). These findings suggest that the association between wine consumption and mortality can not be explained by confounding due to socioeconomic status.

Physical activity

Regular physical activity decreases the risk of cardiovascular diseases, including coronary heart disease (16;17) and stroke (18). Leisure time physical activity is associated with a 12 to 27% reduction in the coronary heart disease risk (19). During the whole follow-up period of the Zutphen Study, different methods were used to quantify physical activity. Therefore, we felt that the available data could not be used in our analyses. However, the lack of adjustment for physical activity could cause residual confounding as it tends to be directly associated with food consumption, especially fruit and vegetables, and dietary fiber intake (20-24). Previous analyses within the Zutphen Study showed that energy intake divided by kg body weight is significantly correlated with physical activity (r=0.35, P-value <.0001) (25). This finding suggested that in epidemiological studies, total energy intake divided by kg body weight can be used as a proxy for physical activity. In our analyses on dietary fiber intake in relation to coronary heart disease and all-cause mortality, we adjusted our models for total energy intake per kg body weight instead of total energy intake and body mass index. Overall conclusions did not change (chapter 6).

Public health relevance

Life expectancy

In epidemiological studies, hazard ratios are commonly used to express the impact on all-cause mortality. Since hazard ratios express effects for an exposed group relative to the effect of the unexposed group, they do not provide information regarding absolute health effects. Such insight can be obtained by the calculation of life expectancies. Life expectancy is the average number of years, calculated for any specified age, a human has before death and is by definition an arithmetic mean, i.e. average survival time. In the Zutphen Study, differences in average survival time or life expectancy at age 50 were estimated by calculating areas under survival curves (26). We used stratified Cox models to obtain the survival curves. For smoking, the models were stratified by categories of smoking status or the number of cigarettes smoked; for alcohol intake, the models were stratified by categories of amount or type of alcoholic beverage. The Cox models were additionally adjusted for baseline covariates, i.e. dietary and smoking variables, BMI, prevalence of chronic diseases, and socioeconomic status. Ninety-five percent confidence intervals were obtained using the bootstrap method (27).

We observed that smoking was positively associated with all-cause mortality and that overall smoking reduced life expectancy at age 50 by 6.5 years (chapter 2). In contrast, light alcohol intake –especially alcohol from wine (chapter 3)– was inversely associated with all-cause mortality and wine consumers had a 5 years longer life expectancy compared to men who do not consume alcohol. The beneficial effects of light to moderate alcohol intake can be explained by a lower risk of cardiovascular mortality (28;29), while smoking not only increases the risk of cardiovascular diseases (30) but also the risk of cancer (31) and COPD (32).

The individual effects of alcohol and smoking are well established, but the joint effect of these lifestyle factors remains unclear. Studies have found that the beneficial effect of moderate alcohol intake on mortality is offset by smoking (33;34). In additional analyses, we estimated the joint effect of wine consumption and overall smoking on all-cause mortality (**figure 7.1**). The HR associated with wine use increased from 0.40 (0.31 to 0.51) for never or long-term former smokers to 0.67 (0.53 to 0.84) for current smokers. Although the interaction between wine use and overall smoking was not statistically significant, the joint effect of wine use and not smoking on mortality was stronger than the sum of the individual effects.

Sudden death

Because 50% of all CHD deaths are sudden, preventing sudden deaths by changes in lifestyle and dietary habits is of great importance for public health. Eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA) –two very long-chain n-3 polyunsaturated fatty acids mainly found in fatty fish– are suggestive for an inverse relation with sudden cardiac death (35;36) because or their anti-arrhythmic properties (37). We observed that long-term fatty fish consumption lowered the risk of sudden coronary death (HR 0.46 [0.27 to 0.78]; chapter 5). In contrast, each 2% increase in long-term energy intake from *trans* unsaturated fatty acids was positively associated with sudden coronary death (HR 1.62 [1.01 to 2.60]; chapter 4). Moreover, dietary fiber intake was not associated with sudden coronary death (unpublished observation).

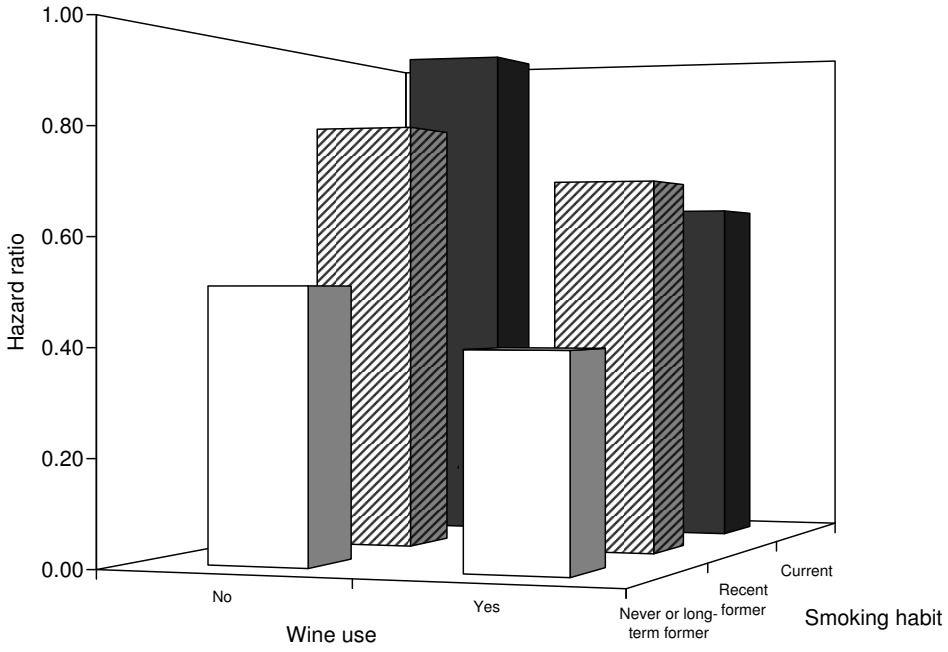

Figure 7.1. Combined effect of long-term wine use and smoking habits on all-cause mortality within the Zutphen Study. Hazard ratios are adjusted for total alcohol intake, former drinker, energy intake without energy from alcohol, body mass index, prevalence of myocardial infarction, diabetes mellitus, stroke, and cancer, and socioeconomic status.

The beneficial effect of n-3 polyunsaturated fatty acids on the risk of sudden cardiac death has been demonstrated, and other fatty acids such as *trans* unsaturated fatty acids have also been associated with sudden cardiac death (38). Lifestyle factors, such as smoking habits and alcohol consumption, may also influence the risk of sudden cardiac death. In subjects with and without a history of coronary heart disease, cigarette smoking was an independent risk factor for sudden cardiac death (39-43). Moreover, smoking cessation significantly reduces the risk of sudden cardiac death (40). In addition, studies have shown associations between alcohol consumption and sudden cardiac death (44). Moderate alcohol intake has been shown to reduce the risk (45), while a high intake may increase the risk of sudden cardiac death (39;46). Generally, lifestyle and dietary risk factors for sudden cardiac death seem to be the same as those for atherosclerotic coronary disease (47).

Future research

The main objective of this thesis was to assess the relationships of recent and long-term exposure to known lifestyle and dietary risk factors with mortality. With the exception of dietary fiber intake, the effects of long-term exposure to the known lifestyle and dietary factors on mortality were stronger than those of recent exposure. However, with the method used to calculate the long-term exposure, it is not possible to assess whether the stronger effects are due to the reduction in measurement error or a greater etiologic relevance. If the long-

term exposure is indeed of greater etiological relevance, this is of great interest for public health recommendations. After all, to profit from dietary or lifestyle habits that have a long-term effect, changes in these habits should be made early in life. So, the challenge for future research would be to separate the effect of reduced measurement error from the etiological relevance when studying long-term exposure. One way to do this is by multiple measurements of dietary and lifestyle habits at each examination round. With this method, the extent of the measurement error due to within-subject variation can be determined and be used to adjust for in future analyses. A number of things should be considered when using such a study design. First, how long should the period between two measurements be. If the intermediate period is too long, you cannot be sure whether the change in exposure is due to measurement error or is a 'real' change. On the other hand, the intermediate period should not be too short to avoid memory effects, i.e. earlier reported values are produced from memory. Second, the period between the examinations also influences the method of data collection. When measuring the exposure repeatedly in a short period of time, the method should be quick and easy to use. Third, how many participants should you include in such a study. A large cohort study has better power, but it will be very difficult, both logistically as well as financially, to examine all participants frequently. Possibly, a subsample of the entire cohort could be used to determine the extent of the measurement error due to within subject variation. Repeated measures of lifestyle and dietary habits can be used to reduce measurement error due to within-subject variation; however, they can not be used to reduce the respondent specific bias in self-reported lifestyle and dietary habits. In future research, data on biomarkers in addition to self-reported information on lifestyle and dietary habits should be used to validate the self-reported values. Obviously, the choice of the most reliable biomarkers is very important in this context (48).

Risk factors for sudden cardiac death are generally the same as those for atherosclerotic coronary disease (47). However, the studies described in this thesis showed that *trans* unsaturated fatty acid intake increased and fatty fish consumption decreased the risk of sudden coronary death, while no associations were found for total CHD death. For fish consumption, Albert *et al.* found in the US Physicians Health Study an association with sudden cardiac death and not with nonsudden cardiac death (49). Therefore, future research on sudden death should focus on identifying risk factors which may specifically predict sudden cardiac death as opposed to nonsudden cardiac death.

Because CHD has been considered a disease predominantly affecting men, women were not included in older prospective cohort studies on CHD. Yet, women have a 30% life-time risk of CHD (50). Most risk factors for CHD are the same for men and women, but the impact of the individual risk factors might be different. Diabetes, HDL cholesterol and triglyceride levels may have a greater impact on CHD risk in women compared to men, while the effects of lipoprotein A seem to be stronger in men (51). The Zutphen Study was performed in men only, and future research is needed to evaluate whether the findings from this thesis are also applicable to women.

Conclusions

The studies described in this thesis emphasize the importance of lifestyle and diet for public health in three ways. First, the results from this thesis suggest that non-smoking and the consumption of a small amount of wine decrease the risk of (cardiovascular) mortality and,

consequently, will increase life expectancy at age 50. However, since alcohol consumption can be addictive, starting to drink because of its positive health benefits can not be recommended. To increase life expectancy at age 50, most attention should be paid to quitting smoking. Second, the consumption of fatty fish and a reduction in *trans* unsaturated fatty acid intake may prevent sudden coronary deaths. Since the intake of *trans* unsaturated fatty acids has already decreased remarkably during the past years, the focus should be on encouraging the consumption of fatty fish for the prevention of sudden coronary deaths. Third, an increase in dietary fiber intake may reduce CHD mortality risk.

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Summary in English

From 1970 through 2007, life expectancy at birth increased steadily from 71 to 78 years among Dutch men. A major determinant for this increase in life expectancy is the decrease in the risk of dying from cardiovascular diseases (CVD). In the Netherlands, cardiovascular diseases are now the second leading cause of death among men. In 2007, about one-third of the men dying from CVD died from coronary heart disease (CHD) and another one-third from cerebrovascular diseases. Moreover, about 50% of the CHD deaths are sudden. The main aim of this thesis is to assess the relationships of recent and long-term exposure to known lifestyle and dietary risk factors with cardiovascular mortality and life expectancy. Data from a prospective cohort study were used to evaluate these relations.

In prospective cohort studies, information on lifestyle and dietary habits is generally only assessed at the baseline examination, assuming that these habits are relatively constant over the follow-up period of the study. Repeated measures can take into account changes in these habits, can reduce measurement error of the exposure as average exposure from multiple measurements has less within-subject variation, and can give more insight into the etiology of diseases. For the studies described in this thesis, we used data from the Zutphen Study, the Dutch contribution to the Seven Countries Study. The Zutphen Study is a prospective cohort study that has been carried out since 1960 among men born between 1900 and 1920. These men were examined repeatedly in seven examination rounds between 1960 and 2000. In every examination round, the men that took part in both the dietary and physical examinations were selected for the studies described in this thesis (n = 1373).

Smoking habits and alcohol consumption are major risk factors for CVD and strong determinants of life expectancy. In **chapter 2**, we described the relationships of long-term cigarette, cigar or pipe smoking, and duration and the number of cigarettes smoked, with cardiovascular mortality and life expectancy. We found that both the number of cigarettes smoked and smoking duration were strongly associated with mortality risk. Compared to never or long-term former smoking, cigarette smoking decreased life expectancy by about 7 years and exclusive cigar or pipe smoking decreased life expectancy by about 5 years. Stopping smoking cigarettes at age 50 increased life expectancy by 3.3 years. The impact of long-term alcohol intake and different types of alcoholic beverages consumed on cardiovascular mortality and life expectancy is estimated in **chapter 3**. We observed that long-term light alcohol intake, i.e. ≤20 grams per day, compared to no alcohol intake, lowered cardiovascular (HR: 0.70 [95% confidence interval: 0.55 to 0.89]) and all-cause (HR: 0.75 [0.63 to 0.91]) mortality risk. Compared to men who do not consume alcohol, wine consumers had a 5 years longer life expectancy.

According to the classic diet-heart hypothesis, saturated fatty acids and dietary cholesterol raise plasma cholesterol levels, thereby causing CHD. More recently, studies have shown that the increased risk of CHD is not only due to an increase in serum cholesterol levels, but also to other factors such as inflammation. Furthermore, the intake of other dietary factors such as *trans* unsaturated fatty acids, fish and dietary fiber may influence the risk of CHD. In **chapter 4**, we describe the changes in *trans* unsaturated fatty acid intake during the 40 years of follow-up of the Zutphen Study. We observed that average intake of *trans* unsaturated fatty acids decreased from 7 to about 1 percent of energy intake between 1960 and 2000. Moreover, we related long-term *trans* unsaturated fatty acids (chapter 4) and fish consumption (**chapter 5**) to (sudden) coronary death. We found that each additional 2 percent of long-term energy intake from *trans*

unsaturated fatty acids was positively associated with sudden coronary death (HR: 1.62 [1.01 to 2.60]). In contrast, long-term fatty fish consumption was inversely associated with sudden coronary death (HR: 0.46 [0.27 to 0.78]). The strength of the association between long-term total fish consumption and CHD death decreased from age 50 (HR: 0.32 [0.13 to 0.80]) until age 80 (HR: 1.34 [0.58 to 3.12]). We observed no clear dose-response relationship between the intake of the n-3 fatty acids EPA and DHA, and (sudden) coronary death. In **chapter 6**, the impact of recent and long-term dietary fiber intake on coronary and all-cause mortality is described. We found that each additional 10 grams of recent dietary fiber intake was associated with a lower risk of CHD (HR: 0.83 [0.70 to 0.98]) and all-cause (HR: 0.91 [0.82 to 1.00]) mortality.

The findings from the studies described in this thesis are put into perspective in **chapter 7**. The main aim of this thesis was to assess the relationships between recent and long-term exposure to known lifestyle and dietary factors on mortality. To better represent long-term exposure to lifestyle and dietary factors, we calculated cumulative average exposures. Averaging repeated measures reduces within-subject variation and, thereby, reduces measurement error. The use of repeated measures may also give more insight into the etiology of diseases. With the exception of dietary fiber intake, the effects of long-term exposure to lifestyle and dietary factors were stronger than those of recent exposure. This suggests that the long-term exposure is etiologically more important than recent exposure. However, this can not be said with certainty, as the stronger effects could also be due to the reduction in measurement error. On the other hand, the stronger effect of recent dietary fiber intake compared with the effects of long-term intake, indicates real etiological relevance of recent intake, as this cannot be explained by the effects of measurement error. Moreover, the use of repeated measures of lifestyle and dietary habits takes into account any changes in these habits during the course of life. It does, however, not reduce the systematic measurement error of the method used for collecting these data.

The findings from our studies emphasize the importance of lifestyle and diet for public health. The individual effects of alcohol and smoking are well established, but the combined effect of these factors on cardiovascular mortality and life expectancy remain unclear. Although the interaction between wine use and overall smoking was not statistically significant, the joint effect of wine use and not smoking on mortality was stronger than the individual effects. However, since alcohol consumption can be addictive, starting to drink because of its positive health benefits can not be recommended and most attention should be paid to quitting smoking. Because 50% of all CHD deaths are sudden, preventing sudden deaths by changes in lifestyle and dietary habits is of great public health importance. The consumption of fatty fish and a reduction in *trans* unsaturated fatty acid intake may prevent sudden coronary death; however, because the intake of *trans* unsaturated fatty acids has decreased remarkably during the past years, the focus should be on encouraging fatty fish consumption.

Future studies on the relationship between long-term exposure to known lifestyle and dietary factors on mortality should focus on separating the effects of reducing the measurement error, by averaging the exposure, from the etiological relevance. Moreover, future research should be done to identify risk factors which may specifically predict sudden coronary death as opposed to nonsudden coronary death and to evaluate whether the findings from this thesis are also applicable to women.

In conclusion, our results suggest that non-smoking and a low level of wine consumption decrease the risk of (cardiovascular) mortality and will increase life expectancy at age 50. The long-term consumption of fatty fish and the reduction in long-term *trans* unsaturated fatty acid intake may prevent sudden coronary deaths, and a higher recent dietary fiber intake may reduce both CHD and all-cause mortality risk.

Summary in Dutch (Samenvatting)

De levensverwachting bij geboorte van Nederlandse mannen is gestaag gestegen van 71 jaar in 1970 tot 78 jaar in 2007. Een belangrijke oorzaak van deze stijging in levensverwachting is de daling in de sterfte aan hart- en vaatziekten, die op dit moment in Nederland de één na belangrijkste doodsoorzaak is onder mannen. Van de mannen die in 2007 overleden aan hart- en vaatziekten, stierf ongeveer een derde als gevolg van coronaire hartziekten en een derde als gevolg van cerebrovasculaire aandoeningen. Daarnaast overlijdt 50% van alle overledenen aan coronaire hartziekten plotseling (plotse hartdood). Het belangrijkste doel van dit proefschrift is het bestuderen van de effecten van een recente en een langdurige blootstelling aan leefstijl en voedingsfactoren op sterfte aan hart- en vaatziekten en de levensverwachting. Voor het bestuderen van deze relaties werden gegevens uit een prospectief cohort onderzoek gebruikt.

In prospectieve cohort studies wordt informatie over leefstijl- en eetgewoonten meestal verzameld aan het begin van het onderzoek, ervan uitgaande dat deze gewoonten relatief constant blijven tijdens het onderzoek. Dit hoeft echter niet altijd zo te zijn. Door het gebruik van herhaalde metingen kan rekening worden gehouden met veranderingen in deze gewoonten in de tijd. Daarnaast kunnen herhaalde metingen de meetfout van de leefstijl- en eetgewoonten verkleinen, aangezien een gemiddelde blootstelling van meerdere metingen een kleinere variatie binnen personen heeft. Ook kan er meer inzicht worden verkregen in het belang van deze factoren voor het ontstaan van ziekten. Voor de onderzoeken die worden beschreven in dit proefschrift, hebben we gebruik gemaakt van gegevens van de Zutphen Studie, de Nederlandse bijdrage aan de Zeven Landen Studie. De Zutphen Studie is een prospectief cohort onderzoek dat is uitgevoerd vanaf 1960 onder mannen die geboren zijn tussen 1900 en 1920. Tussen 1960 en 2000 zijn deze mannen zeven keer onderzocht. Voor de onderzoeken in dit proefschrift, zijn de mannen geselecteerd die in een meetronde zowel aan het voedingsonderzoek als ook aan het lichamelijk onderzoek hebben meegedaan (n = 1373).

Roken en alcoholgebruik zijn belangrijke risicofactoren voor sterfte aan hart- en vaatziekten en sterke determinanten van de levensverwachting. In **hoofdstuk 2** hebben we de effecten van het langdurig roken van sigaretten, sigaar of pijp, en van de duur en het aantal gerookte sigaretten, op sterfte aan hart- en vaatziekten en levensverwachting beschreven. Wij zagen dat zowel het aantal gerookte sigaretten als het aantal jaren dat er sigaretten werden gerookt, sterk geassocieerd waren met het sterfterisico. Vergeleken met mannen die nooit rookten of reeds een lange tijd gestopt waren met roken, was de levensverwachting van de mannen die sigaretten rookten ongeveer 7 jaar korter; voor mannen die alleen sigaar of pijp rookten was dit ongeveer 5 jaar. Door te stoppen met het roken van sigaretten op 50-jarige leeftijd nam de levensverwachting met 3,3 jaar toe. De gevolgen van een langdurige inname van alcohol en consumptie van verschillende soorten alcoholische dranken op sterfte aan hart- en vaatziekten en levensverwachting zijn beschreven in **hoofdstuk 3**. Langdurig licht alcoholgebruik, d.w.z. ≤20 gram per dag (≤2 glazen per dag), verlaagde, vergeleken met geen alcoholgebruik, het risico op sterfte aan hart- en vaatziekten (Hazard Ratio [HR]: 0,70 [95% betrouwbaarheidsinterval: 0,55 tot 0,89]) en het risico op totaal sterfte (HR: 0,75 [0,63 tot 0,91]). Vergeleken met mannen die geen alcohol gebruiken hadden wijn drinkers een 5 jaar hogere levensverwachting.

De klassieke ‘voeding-hartinfarct’ hypothese gaat ervan uit dat verzadigde vetzuren en voedingscholesterol het cholesterolgehalte in het bloed verhogen waardoor het risico op het krijgen van coronaire hartziekten groter wordt. Recentelijk hebben studies aangetoond dat het verhoogde risico op coronaire hartziekten niet alleen te wijten is aan een toename van

het cholesterolgehalte in het bloed, maar ook aan andere factoren, zoals ontstekingprocessen. Bovendien kan de inname van andere voedingsfactoren, zoals *trans* onverzadigde vetzuren, vis en voedingsvezel, ook van invloed zijn op het ontstaan van coronaire hartziekten. In **hoofdstuk 4** beschrijven wij de veranderingen in de inname van *trans* onverzadigde vetzuren tijdens de 40 jarige onderzoeksperiode van de Zutphen Studie. Tussen 1960 en 2000 is de gemiddelde inname van *trans* onverzadigde vetzuren gedaald van 7 tot ongeveer 1 procent van de totale energie inname. Daarnaast hebben wij gekeken of er een verband was tussen de langdurige inname van *trans* onverzadigde vetzuren (hoofdstuk 4) en de consumptie van vis (**hoofdstuk 5**) en (plotselinge) sterfte aan coronaire hartziekten. Wij vonden dat iedere 2 procent extra aan langdurige inname van energie uit *trans* onverzadigde vetzuren was geassocieerd met een hoger risico op plotse hartdood (HR: 1,62 [1,01 tot 2,60]). In tegenstelling tot de inname van *trans* onverzadigde vetzuren, was de langdurige consumptie van vette vis geassocieerd met een lager risico op plotse hartdood (HR: 0,46 [0,27 tot 0,78]). De sterkte van het verband tussen de langdurige consumptie van vis en sterfte aan coronaire hartziekten nam af van 50-jarige (HR: 0,32 [0,13 tot 0,80]) tot 80-jarige leeftijd (HR: 1,34 [0,58 tot 3,12]). We zagen geen duidelijke dosis-respons relatie tussen de inname van de n-3 vetzuren uit vis (EPA en DHA) en (plotselinge) sterfte aan coronaire hartziekten. In **hoofdstuk 6** wordt het verband van een recente en een langdurige inname van voedingsvezel met sterfte aan coronaire hartziekten en totaal sterfte beschreven. Elke 10 gram extra recente inname van voedingsvezel was geassocieerd met een lager risico op sterfte aan coronaire hartziekten (HR: 0,83 [0,70 tot 0,98]) en totaal sterfte (HR: 0,91 [0,82 tot 1,00]).

De resultaten van dit onderzoek worden in perspectief geplaatst in **hoofdstuk 7**. Het belangrijkste doel van dit proefschrift was om de verbanden van een recente en een langdurige blootstelling aan leefstijl en voedingsfactoren met sterfte te bestuderen. Om een langdurige blootstelling aan leefstijl en voedingsfactoren beter weer te geven, hebben wij een cumulatief gemiddelde blootstelling berekend. Door het middelen van herhaalde metingen vermindert de variatie van de blootstelling binnen personen, met als gevolg dat de meetfout van de blootstelling kleiner wordt. Door het gebruik van herhaalde metingen kan ook beter inzicht in het ontstaan van ziekten worden verkregen. Met uitzondering van de inname van voedingsvezel, waren de effecten van een langdurige blootstelling aan leefstijl en voedingsfactoren sterker dan die van een recente blootstelling. Dit suggereert dat een langdurige blootstelling belangrijker is voor het sterfterisico dan een recente blootstelling. Dit kan echter niet met zekerheid worden vastgesteld, aangezien de sterkere relaties van een langdurige blootstelling met sterfte ook het gevolg kunnen zijn van de verkleining van de meetfout. Aan de andere kant, het sterkere verband van de recente inname van voedingsvezel, in vergelijking met die van een langdurige inname, geeft aan dat de recente inname van voedingsvezel belangrijker is voor het sterfterisico, aangezien dit niet kan worden verklaard door effecten van de meetfout. Daarnaast kan door het gebruik van herhaalde metingen rekening worden gehouden met veranderingen van leefstijl en eetgewoonten tijdens de onderzoeksperiode. De herhaalde metingen bieden echter geen oplossing voor de systematische meetfout van de gebruikte methodes voor het verzamelen van deze gegevens.

De bevindingen van onze onderzoeken benadrukken het belang van leefstijl en voeding voor de volksgezondheid. De afzonderlijke effecten van alcohol en roken zijn goed beschreven, maar het gecombineerde effect van deze factoren op sterfte aan hart- en vaatziekten en

levensverwachting is nog onduidelijk. Hoewel de interactie tussen wijn consumptie en roken niet statistisch significant was, was het gezamenlijke effect van wijn consumptie en niet-roken op sterfte sterker dan de afzonderlijke effecten. Echter, aangezien de consumptie van alcohol verslavend kan zijn, kan het beginnen met drinken vanwege de positieve gezondheidseffecten niet worden aanbevolen en zal in preventie programma's de meeste nadruk moeten worden gelegd op het stoppen met roken. Omdat 50% van de sterfte aan coronaire hartziekten plotseling plaatsvindt (plotse hartdood), is het voorkomen van plotse hartdood door veranderingen in leefstijl en eetgewoonten ook van groot belang voor de volksgezondheid. Onze resultaten laten zien dat de consumptie van vette vis en een verminderde inname van *trans* onverzadigde vetzuren plotselinge hartdood kan voorkomen. Echter, omdat de inname van *trans* onverzadigde vetzuren al opmerkelijk daalde in de afgelopen jaren, zal de nadruk moeten liggen op het stimuleren van vette vis consumptie.

In hoofdstuk 7 worden ook suggesties gegeven voor toekomstig onderzoek naar de relaties tussen langdurige blootstelling aan bekende leefstijl en eetgewoonten en sterfte. Toekomstig onderzoek zou zich moeten richten op het uit elkaar halen van de effecten van de verkleining van de meetfout, als gevolg van het gebruik van een gemiddelde blootstelling, en de meest relevante blootstellingperiode voor het ontstaan van ziekten en het sterfterisico. Bovendien zal gezocht moeten worden naar risicofactoren die specifiek plotselinge sterfte aan coronaire hartziekten (plotse hartdood) voorspellen in tegenstelling tot sterfte aan chronisch verlopende coronaire hartziekten. Daarnaast zal bekeken moeten worden of de bevindingen uit dit proefschrift ook van toepassing zijn op vrouwen.

Kortom, onze resultaten suggereren dat niet-roken en een lage consumptie van wijn de kans op sterfte aan hart- en vaatziekten verlaagt en de levensverwachting op 50 jarige leeftijd verhoogt. Langdurige consumptie van vette vis en vermindering van de langdurige inname van trans onverzadigde vetzuren kunnen plotse hartdood voorkomen. Bovendien kan een hogere inname van voedingsvezel de kans op sterfte aan coronaire hartziekten en totaal sterfte verkleinen.

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Martinet

About the author

Curriculum Vitae

Martinette Terese (Martinet) Streppel was born on September 23rd 1980 in Deventer, The Netherlands. After passing secondary school (Hoger Algemeen Voortgezet Onderwijs) at the Geert Groote College in Deventer (1997), she attended the Hanze University Groningen (Hanzehogeschool Groningen) to obtain her BSc degree in Nutrition and Dietetics (2001). During her final thesis work, she was introduced to the field of nutritional research at the Wageningen University and decided to continue her education there at the Division of Human Nutrition. In 2003, Martinet completed her final thesis entitled: 'The effect of fibre supplementation on blood pressure: a meta-analyses of randomized controlled trials' and received her MSc degree with a major in Human Epidemiology. Shortly after graduation, she started working as a PhD fellow at the same university. During her PhD, she attended several conferences and courses within the education programme of the VLAG graduate school. The research described in this thesis was primarily performed at the National Institute for Public Health and the Environment (RIVM) in Bilthoven. Since May 2008, Martinet is appointed as a postdoctoral fellow at Top Institute Food and Nutrition, Wageningen, to perform research on diet and early changes in endothelial function.

List of publications

Articles in scientific journals

- **Streppel MT**, Ocké MC, Boshuizen HC, Kok FJ, Kromhout D. Long-term wine consumption is indepently of alcohol consumption related to cardiovascular mortality and life expectancy: The Zutphen Study. J Epidemiol Community Health, accepted for publication.
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- Buijsse B, Boer JMA, **Streppel MT**, Ocké MC, Savelkoul M, Wendel-Vos W, Verhagen H. Epidemiologische aspecten van ischemische hartziekten in relatie tot voeding. Informatorium voor Voeding en Dietetiek, Dieetleer 3A. Bohn Stafleu en Loghum: Houten, december 2007.
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Overview of completed training activities

Discipline specific courses

- Methodological and Statistical Aspects of Longitudinal Research, CaRe, Nijmegen (NL), 2004
- Survival Analysis, Erasmus Summer Programme, Rotterdam (NL), 2004
- Principles of Research in Medicine and Epidemiology, Erasmus Summer Programme, Rotterdam (NL), 2004
- Introduction to Public Health, Erasmus Summer Programme, Rotterdam (NL), 2004
- Methods of Public Health Research, Erasmus Summer Programme, Rotterdam (NL), 2004
- Public Health Research Methods – Analysis of Population Health, NIHES, Rotterdam (NL), 2004
- Public Health Research Methods – Analysis of Determinants, NIHES, Rotterdam (NL), 2004
- Nutrition and Lifestyle Epidemiology, VLAG, Wageningen (NL), 2005
- Vascular Biology, Netherlands Platform for Cardiovascular Research of the Netherlands Heart Foundation, Arnhem (NL), 2005

National and international conferences

- Conference on Epidemiological Longitudinal Studies in Europe (CELSE), Bristol (UK), 2004
- European Congress of Epidemiology, Utrecht (NL), 2006
- 47th Annual Conference on CVD Epidemiology and Prevention, Orlando, Florida (USA), 2007
- NWO Nutrition, Arnhem and Deurne (NL), 2003, 2005-2007

General courses

- PhD Week, VLAG, Bilthoven (NL), 2004
- Talent Day, NWO, Utrecht (NL), 2006
- Scientific Writing, CENTA/WUR, Wageningen (NL), 2004
- Presentation Skills, CENTA/WUR, Wageningen (NL), 2005
- Organizing and Supervising MSc Thesis Projects, WUR, Wageningen (NL), 2005

Optional courses and activities

- Preparation PhD Research Proposal, WUR, Wageningen (NL), 2003
- PhD Tour to Australia, 2003
- PhD Tour to England, Ireland, and Scotland, 2005
- Literature Study Programme Division of Human Nutrition, WUR, Wageningen (NL), 2004-2006
- CVG Lectures, RIVM, Bilthoven (NL), 2003-2007

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